

Prediction of Early Neurological Deterioration in Individuals With Minor Stroke and Large Vessel Occlusion Intended for Intravenous Thrombolysis Alone

Pierre Seners, Wagih Ben Hassen, Bertrand Lapergue, Caroline Arquizan, Mirjam Rachel Heldner, Hilde Henon, Claire Perrin, Davide Strambo, Jean-Philippe Cottier, Denis Sablot, et al.

▶ **To cite this version:**

Pierre Seners, Wagih Ben Hassen, Bertrand Lapergue, Caroline Arquizan, Mirjam Rachel Heldner, et al.. Prediction of Early Neurological Deterioration in Individuals With Minor Stroke and Large Vessel Occlusion Intended for Intravenous Thrombolysis Alone. JAMA neurology, 2021, Online ahead of print. 10.1001/jamaneurol.2020.4557 . inserm-03108984

HAL Id: inserm-03108984
https://inserm.hal.science/inserm-03108984

Submitted on 13 Jan 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Prediction of early neurological deterioration in minor stroke with large vessel occlusion intended for intravenous thrombolysis alone

Pierre SENERS,[1] MD; Wagih BEN HASSEN,[2] MD; Bertrand LAPERGUE,[3] MD; Caroline ARQUIZAN,[4] MD; Mirjam R. HELDNER,[5] MD; Hilde HENON,[6] MD; Claire PERRIN,[1] MSc; Davide STRAMBO,[7] MD; Jean-Philippe COTTIER,[8] MD; Denis SABLOT,[9] MD; Isabelle GIRARD BUTTAZ,[10] MD; Ruben TAMAZYAN,[11] MD; Cécile PRETERRE,[12] MD; Pierre AGIUS,[12,13] MD; Nadia LAKSIRI,[14] MD; Laura MECHTOUFF,[15] MD; Yannick BEJOT,[16] MD; Duc-Long DUONG,[17] MD; François MOUNIER-VEHIER,[18] MD; Gioia MIONE,[19] MD; Charlotte ROSSO,[20] MD; Ludovic LUCAS,[21] MD; Jérémie PAPASSIN,[22,23] MD; Andrea AIGNATOAIE,[24] MD; Aude TRIQUENOT,[25] MD; Emmanuel CARRERA,[26] MD; Philippe NICLOT,[27] MD; Alexandre OBADIA,[28] MD; Aïcha LYOUBI,[29] MD; Pierre GARNIER,[30] MD; Nicolae CRAINIC,[31] MD; Valérie WOLFF,[32] MD; Clément TRACOL,[33] MD; Frédéric PHILIPPEAU,[34] MD; Chantal LAMY,[35] MD; Sébastien SOIZE,[36] MD; Jean-Claude BARON,[1] MD*; Guillaume TURC,[1] MD*; on behalf of the MINOR-STROKE collaborators.

1: Neurology Department, GHU Paris psychiatrie et neurosciences, Institut de Psychiatrie et Neurosciences de Paris (IPNP), INSERM U1266, Université de Paris, FHU Neurovasc, Paris, France.
2: Radiology Department, GHU Paris psychiatrie et neurosciences, Institut de Psychiatrie et Neurosciences de Paris (IPNP), INSERM U1266, Université de Paris, FHU Neurovasc, Paris, France.
3: Neurology Department, Foch University Hospital, Suresnes, France.
4: Neurology Department, CHRU Gui de Chauliac, Montpellier, France.
5: Neurology Department, Inselspital, University Hospital and University of Bern, Bern, Switzerland.
6: Neurology Department, CHU Lille, Université de Lille, INSERM U1171, Lille, France.
7: Stroke Center, Neurology Service, CHU Vaudois, Lausanne University, Lausanne, Switzerland
8: Neurology Department, Bretonneau Hospital, Tours, France.
9: Neurology Department, Perpignan Hospital, Perpignan, France.
10: Neurology Department, Valenciennes Hospital, Valenciennes, France.
11: Neurology Department, Saint Joseph Hospital, Paris, France.
12: Neurology Department, Nantes University Hospital, Nantes, France.
13: Neurology Department, St Nazaire Hospital, France.
14: Neurology Department, La Timone University Hospital, Marseille, France.
15: Department of Stroke Medicine, Hospices Civils de Lyon, Lyon, France.
16: Neurology Department, Dijon University Hospital, Dijon, France.
17: Neurology Department, Versailles University Hospital, Versailles, France.
18: Neurology Department, Lens Hospital, Lens, France.
19: Neurology Department, Nancy University Hospital, Nancy, France.
20: Sorbonne Université, Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS UMR 7225, AP-HP ; Urgences Cérébro-Vasculaires ; ICM infrastructure stroke network, Hôpital Pitié-Salpêtrière, F-75013, Paris, France.
21: Stroke Unit, Bordeaux University Hospital, Bordeaux, France.
22: Stroke Unit, Grenoble University Hospital, Grenoble, France.
23: Neurology department, Centre Hospitalier Metropole-Savoie, Chambery, France.
24: Neurology department, Centre Hospitalier Régional d'Orléans, Orléans, France.
25: Neurology Department, CHU Rouen, F-76000 Rouen, France.
26: Neurology Department, Geneve University Hospital, Geneve, Switzerland.
27: Neurology Department, René Dubos Hospital, Pontoise, France.
28: Neurology Department, Fondation Adolphe de Rothschild, Paris, France.
29: Neurology Department, Delafontaine Hospital, Saint-Denis, France.
30: Stroke Unit, Saint-Etienne University Hospital, Saint-Etienne, France.

31: Neurology Department, Brest University Hospital, Brest, France.
32: Neurology Department, Strasbourg University Hospital, Strasbourg, France.
33: Neurology Department, Rennes University Hospital, Rennes, France.
34: Neurology Department, Fleyriat Hospital, Bourg-en-Bresse, France.
35: Neurology Department, Amiens University Hospital, Amiens, France.
36: Neuroradiology Department, Reims University Hospital, Reims, France.

*These authors share senior authorship.

MINOR-STROKE collaborators: Sonia ALAMOWITCH, Charles ARTEAGA, Omar BENNANI, Yves BERTHEZENE, Marion BOULANGER, Claire BOUTET, Serge BRACARD, Nicolas BRICOUT, Hervé BRUNEL, Serkan CAKMAK, Olivier CHASSIN, Mohamed CHBICHEB, Frédéric CLARENÇON, Vincent COSTALAT, Audrey COURSELLE-ARNOUX, Séverine DEBIAIS, Mathilde DELPECH, Christian DENIER, Hubert DESAL, Olivier DETANTE, Gauthier DULOQUIN, Laurie FRATICELLI, Sébastien GAZZOLA, Jan GRALLA, Valer GRIGORAS, Benoit GUILLON, Matthieu KRUG, Steven HAJDU, Simon JUNG, Frédéric KLAPCZYNSKI, Didier LEYS, François LUN, Arnaud MALBRANQUE, Sébastien MARCEL, Patrik MICHEL, Jean-Louis MAS, Mylène MASSON, Norbert NIGHOGHOSSIAN, Michael OBADIA, Catherine OPPENHEIM, Canan OZSANCAK, Fernando PICO, Michel PIOTIN, Christine PIRES, Sébastien RICHARD, Yves SAMSON, Isabelle SERRE, Igor SIBON, Philippe SMADJA, Laurent SPELLE, Laurent SUISSA, Serge TIMSIT, Emmanuel TOUZÉ, Amélie TUFFAL, Anne-Evelyne VALLET, Marion YGER, Stéphane VANNIER, Mathieu ZUBER.

Correspondence to Dr. Pierre Seners, Neurology Department, Sainte-Anne Hospital, 1, rue Cabanis, 75014 Paris, France. E-mail: pierre.seners@gmail.com
Phone: 33 1 45 65 87 34. Fax: 33 1 45 65 87 94

Manuscript word count (not including title, abstract, references, tables, and figure legends): 3013

Number of tables: 3; Number of figures: 3.

Key Points:

Question: Is early neurological deterioration of ischemic origin (END_i) predictable in minor strokes with large vessel occlusion (LVO) treated with intravenous thrombolysis (IVT)?

Findings: In a multicentric retrospective cohort of minor stroke patients (NIHSS≤5) with LVO intended for IVT alone (n=729), an easily applicable score based on occlusion site and thrombus length –two independent predictors of END_i– showed good discriminative power for END_i risk prediction, and was successfully validated in an independent cohort (n=347).

Meaning: END_i can be reliably predicted in IVT-treated minor strokes with LVO, which may help to select the best candidates for direct transfer for additional thrombectomy.

Abstract

Importance: What is the best reperfusion strategy in acute minor stroke with large vessel occlusion (LVO) is unknown. Accurately predicting early neurological deterioration of presumed ischemic origin (END_i) following intravenous thrombolysis (IVT) in this population may help to select candidates for immediate transfer for additional thrombectomy.

Objective: To develop and validate an easily applicable predictive score of END_i following IVT in minor stroke with LVO.

Design, setting and participants: Multicentric retrospective cohort of consecutive minor stroke patients (NIHSS score≤5) with LVO (basilar artery, internal carotid artery [ICA], first [M1] or second [M2] segment of middle cerebral artery) intended for IVT alone in 45 French stroke centres, *i.e.*, including those who eventually received rescue thrombectomy because of END_i. For external validation, another cohort with similar inclusion criteria was collected from 9 additional centres.

Main Outcome and Measure: END_i, defined as ≥4pts deterioration on NIHSS score within the first 24hrs without parenchymal haemorrhage on follow-up imaging or another identified cause.

Results: In the derivation cohort, 729 patients were included. Mean age was 70±15yrs, median NIHSS score was 3, and occlusion site was ICA, M1, M2, and basilar artery, in 97 (13%), 207 (28%), 395 (54%), and 30 (4%) patients, respectively. END_i occurred in 88 (12%, 95%CI 10-14) patients and was strongly associated with poorer 3-month outcome, even in patients who underwent rescue thrombectomy. In multivariable analysis, a more proximal occlusion site (P<0.001) and a longer thrombus (P=0.002) were independently associated with END_i. A 4-point score derived from these variables –1 point for thrombus length and 3 points for occlusion site– showed good discriminative power for END_i (c-statistic=0.76; 95%CI:0.70-0.82), and was successfully validated in the validation cohort (n=347; END_i rate: 11%; c-statistic=0.78). In both cohorts, END_i probability was ~3%, ~7%, ~20%, and ~35% for scores 0, 1, 2 and 3-4, respectively.

Conclusions and Relevance: The substantial END_i rates observed in our cohorts highlights the current debate regarding whether to directly transfer IVT-treated minor stroke patients with LVO for additional thrombectomy. Based on the strong associations observed, we derived and externally validated an easily applicable score for END_i risk prediction that may assist decision-making.

Introduction

Likely owing to good collaterals, a sizeable fraction of acute stroke patients with large vessel occlusion (LVO) presents with only mild neurological deficit. Although intravenous thrombolysis (IVT) is standard-of-care in minor but disabling stroke with LVO,[1] the substantial risk of early neurological deterioration (END) and poor 3-month outcome has been repeatedly underlined.[2-4] Given that END is rarely due to intracranial haemorrhage in this population, it is presumed "of ischemic origin" (END_i) in most patients, yet the precise underlying mechanisms are incompletely deciphered.[2,5] Considering the strong association between lack of recanalization and END_i in unselected stroke populations,[6,7] bridging therapy (*i.e.*, IVT followed by mechanical thrombectomy [MT]) may be an attractive option for minor stroke with high END_i risk. However, although bridging therapy is currently recommended in non-minor LVO patients eligible for IVT (i.e., with National Institutes of Health Stroke Scale (NIHSS) score >5), whether it is superior to IVT alone in minor stroke with LVO is unknown because few such patients were enrolled in the pivotal thrombectomy trials.[8]

Here, we aimed to i) identify the incidence and predictors of END_i in a large sample of patients with IVT-treated LVO minor stroke, and, from there, ii) develop and externally validate a prediction score intended to assist clinicians in assessing the risk of END_i in this population, and in turn in selecting the most appropriate candidates for bridging therapy.

Methods

Study design and data sources

Derivation cohort

The MINOR-STROKE collaboration[9] retrospectively collected the data from all consecutive acute stroke patients admitted to 45 French stroke centres between 2006 and 2018 (inclusion dates varied among centres, see **eTable 1**) who fulfilled the following criteria: (1) baseline admission NIHSS score ≤5; (2) LVO on pre-treatment vascular imaging (internal carotid artery [ICA], first [M1] or second [M2] segment of middle cerebral artery [MCA], basilar artery), and (3) treated with IVT (alteplase only), with or without additional MT. In all the participating centres, vascular imaging (MR-angiography [MRA] or CT-angiography [CTA]) was systematically performed on admission for acute stroke patients admitted within a reperfusion time-window during the inclusion time-period, irrespective of symptom severity.

In the present study we focused on patients with MCA or basilar artery occlusion intended for IVT alone, *i.e.* including those who eventually received rescue MT because of END_i. Therefore, we excluded the patients (1) directly intended for additional MT, or (2) with isolated ICA occlusion (*i.e.*, without MCA occlusion).

Validation cohort

We used the prospectively gathered databases of 9 additional stroke centers (6 from France and 3 from Switzerland, **eTable 1**). To construct this cohort, the same inclusion criteria as above were applied.

Each patient was informed of his/her participation in the study. In accordance with local legislation, 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 and radiological data

Clinical variables routinely recorded in the acute stroke setting were collected (**Supplemental Methods**). All included patients underwent either CT with CTA or MRI with MRA before IVT start, and follow-up MRI or CT within ~24hrs following admission. Perfusion imaging (CT- or MR-

perfusion) was part of routine admission protocol in some centers. Additional MRI or CT was also obtained in case of END. In the derivation cohort, to ensure homogeneity in radiological evaluation, one stroke neurologist reviewed all pre-IVT and follow-up imaging, and MT procedures of all included patients, blinded to clinical outcomes. The following variables were collected (see **Supplemental Methods** for details): (1) occlusion site, divided into the following categories: intracranial T or L ICA (ICA-T/L), proximal M1, distal M1, M2, tandem cervical ICA and M1 or M2, and basilar artery; (2) thrombus length measured either on MRI (*i.e.*, susceptibility vessel sign), on CT (hyperdense MCA sign) or on CTA;[10-12] (3) infarct core extent; and (4) whenever perfusion imaging was available, the severity of hypoperfusion was assessed using the hypoperfusion intensity ratio (HIR).[13] For patients receiving groin puncture (*i.e.*, rescue MT), recanalization was evaluated on the final intracranial run using the modified Thrombolysis in Cerebral Infarction (mTICI) scale. mTICI 2b-3 was considered as successful recanalization. The same methodology was applied for the validation cohort, with central imaging reading for 4 out of 9 participating centers.

Definition of END_i

END_i refers to neurological deterioration "of presumed ischemic origin", *i.e.*, the only END category that may be prevented by MT, and was defined as an NIHSS score increase ≥4 points within the first 24 hours after IVT[5,6] without evidence of a parenchymal hemorrhage according to the European Cooperative Acute Stroke Study definition on follow-up imaging or with no identified alternative cause (*e.g.*, post-stroke seizure) after careful review of the medical records by a local stroke physician.[7]

Statistical analysis

Continuous variables were described as mean±standard deviation or median (interquartile range), as appropriate, and categorical variables as numbers and percentages. In the derivation cohort, we modeled the probability of a worse 3-month functional outcome in patients with and without END_i via an ordinal logistic regression, providing a common Odds Ratio (cOR) and its 95% confidence interval (95%CI) across the whole range of the mRS. The procedures used to identify predictors of END_i, derive and externally validate a predictive score are detailed in the **Supplemental Methods**. Briefly,

stepwise multivariable binary logistic regression analysis was conducted in the derivation cohort with END_i as dependent variable. Two different models were derived, with and without thrombus length as this variable was not available for all patients. The END_i score was derived based on the multivariable model above with the highest c-statistic. Discrimination of the score to predict END_i was assessed using c-statistic. Internal cross-validation was performed using the bootstrap method and external validation was performed on the validation cohort.

Results

Study population

A total of 729 and 347 patients were included in the derivation and validation cohorts, respectively (see flow-chart in **eFigure 1**). Baseline characteristics of patients from the derivation and validation cohorts are provided in **Table 1**.

END incidence, causes and characteristics

In the derivation cohort, END occurred in 96 (13.2%, 95%CI 10.7-15.7) patients and was of presumed ischemic origin in 88 (END_i: 12.1%, 95%CI 9.7-14.4, see details in Table 1). Median NIHSS score increase in END_i patients was 8 (IQR 5-14), and the timing of END_i after IVT start was within 2, 2 to 6, 6 to 12, and 12 to 24 hours in 48%, 13%, 8%, and 32% patients, respectively. Among END_i patients, 49/88 (56%) underwent rescue MT, with groin puncture occurring at a median delay of 95min following END_i (IQR 70-150), and successful reperfusion (mTICI 2b-3) obtained in 40/49 (82%) patients. Further details regarding the timeline and MT procedures, and baseline comparison of END_i patients treated with or without rescue MT are provided in **eTable 2**. As compared to END_i patients without rescue MT, those with rescue MT were more frequently treated after 2014 and had shorter IVT-to-END_i delays. In the validation cohort, END_i occurred in 38 (11.0%, 95%CI 7.7-14.3) patients (see Table 1 for details).

Outcome according to END_i status in the derivation cohort

Patients with END_i had significantly poorer 3-month outcome than those without (cOR=7.37, 95%CI 4.79-11.35, P<0.0001, **Figure 1A**). The rate of excellent functional outcome (mRS<2) was 34% and 78% in patients with and without END_i, respectively (P<0.0001). END_i patients treated with rescue MT had better outcome than those without (cOR= 3.72, 95%CI 1.67-8.32, P=0.001; **Figure 1B**). The rate of excellent functional outcome was 48% and 16% in END_i patients with and without rescue MT, respectively (P=0.002). END_i patients with rescue MT had lower rates of excellent functional outcome than patients without END_i (48% and 78%, respectively, P<0.001).

Predictors of END_i in the derivation cohort

Univariable analysis

The baseline characteristics of patients with and without END_i and the results of the univariable analyses are presented in **Table 2**. Patients experiencing END_i were more frequently men, had more proximal occlusion and longer thrombus. Perfusion parameters, including HIR, were not associated with END_i. The effect of thrombus length on END_i was similar for patients with baseline MRI and CT/CTA (unadjusted OR=1.11 [95%CI 1.06-1.16] and 1.12 [95%CI 0.98-1.29] per 1-mm increase, respectively, *P* for interaction=0.83). **Figure 2** illustrates the END_i rate according to occlusion site and the END_i predicted probability as a function of thrombus length.

Multivariable analysis

After stepwise variable selection into the multivariable model using the variables with $P<0.20$ from Table 2 except for thrombus length, occlusion site was the sole variable associated with END_i (model 1, **Table 3**).

The alternative multivariable model including thrombus length as a continuous variable revealed that both occlusion site ($P<0.001$) and thrombus length ($P=0.002$) were independently associated with END_i. We then dichotomized thrombus length using the Youden index for END_i prediction as cutoff (namely, thrombus length <9mm and ≥9mm). This multivariable model is presented in **Table 3** (model 2). There was no interaction between thrombus length and occlusion site for END_i prediction, *i.e.*, the effect of thrombus length on END_i did not differ across occlusion sites. The c-statistic of model 2 was significantly higher than model 1 (0.77, 95%CI 0.71-0.83 and 0.72, 95%CI 0.66-0.78, respectively, $P=0.006$ for comparison).

The sensitivity analyses of the two models for patients treated before and since 2015 are presented in **eTable 3**. The results were similar for each time period.

END_i prediction score

Derivation of the score

We used model 2 for the derivation of the END_i score because it was associated with the highest c-statistic. The integer-based score (range: 0-4 points) was constructed according to the magnitude of the

regression coefficients observed in model 2 (**Figure 3**). The probability of END_i per incremental point of the score is shown in **Figure 3**: END_i probability was <7% for scores 0 or 1 –which represents two-thirds of the overall sample– but was >18% for scores 2 to 4, reaching 35% for score 3 or 4. The c-statistic of the score was 0.76 (95%CI: 0.70-0.82).

Score validation

The internal cross-validation based on 2,000 bootstrap replicates showed a similar c-statistic (0.75, 95%CI 0.69-0.82). In the external validation cohort, the END_i score showed good discrimination (c-statistic 0.78, 95% CI: 0.70–0.86) and calibration (Figure 3; Hosmer-Lemeshow test P=0.78) to predict END_i.

Discussion

Based on two large multicentric cohorts of minor stroke with LVO, this study disclosed 4 key findings: (1) END_i affected ~12% of patients and accounted for ~90% of END cases; (2) 3-month functional outcome following END_i improved with rescue MT but remained overall poor; (3) in multivariable analysis, more proximal occlusion and longer thrombus were independently associated with END_i; and (4) the derived END_i score had good discriminative power, and was successfully validated in an independent cohort.

Cause of END

In both cohorts, END_i accounted for ~90% patients with END following IVT. Indeed, symptomatic intracranial haemorrhage occurred in <7% of END cases –which is expected considering the mild baseline symptoms and small baseline infarct core– and a clear alternative cause was identified in only 3-7% of all ENDs, in line with previous studies.[2,3,5] As our ultimate aim here was to help physicians select the most appropriate candidates for immediate transfer for thrombectomy following IVT, we will focus on END_i in what follows.

Incidence of END_i and relationships with outcome

Thus far, a single previous study has focused on END_i in IVT-treated minor stroke patients with LVO, reporting a slightly lower incidence rate than in the present study (9% *vs*. 12%, respectively).[2] This difference is likely explained by the a priori exclusion in this study[2] of patients receiving rescue MT (*i.e*., MT performed because of END_i). Importantly, consistent with earlier studies,[2,7,14] END_i was found here to be strongly associated with poor functional outcome. Even though excellent functional outcome was more frequent in rescue MT *vs.* no rescue MT patients (48% *vs.* 16%, respectively), the former subset had significantly poorer outcome than patients without END_i (78%), despite successful reperfusion obtained in 82% of cases. This observation is consistent with a previous study in similar population.[15] Note that, due to non-invasive brain imaging being performed on site to rule out intracranial hemorrhage, the time elapsed between END_i and groin puncture was substantial in our study (median: 95min), which may in part explain the poor outcomes observed despite rescue MT. Considering that END is of presumed ischemic origin in 90% of patients in this population, direct

transfer to the angiosuite –*i.e.*, bypassing non-invasive brain imaging– might therefore be an option to reduce this delay, particularly in mothership patients.

The substantial incidence of post-IVT END_i together with its strong association with poor outcome even despite rescue MT shed new light on current debates regarding management of minor stroke with LVO, particularly whether immediate transfer for MT following IVT should be considered in these patients. As minor strokes were excluded a priori from the pivotal thrombectomy trials,[8] the benefits from bridging therapy remain unknown in this population for which current guidelines regarding thrombectomy are somewhat vague ("may be reasonable").[1,8] Randomized trials testing MT added on best medical management *vs.* best medical management alone in this population are underway (ENDO-LOW [NCT04167525] and In Extremis/MOSTE [NCT03796468]). However, because of the mild baseline clinical severity and overall good 3-month outcome following IVT alone in this population, large samples will be required to show significant superiority of bridging therapy –a major challenge considering the relative rarity of minor stroke with LVO. As patients at higher END_i risk may benefit from direct transfer for additional thrombectomy, our next aim was to identify independent predictors of END_i.

Independent predictors of END_i

Two independent predictors of END_i emerged from the present study. The first was more proximal occlusion site, in line with the single previous comparable study[2] as well as with earlier studies in non-thrombolysed minor stroke patients[16,17] and non-minor IVT-treated patients.[6,7,18] The second independent predictor of END_i was thrombus length, such that the longer the thrombus the higher the odds of END_i. To our knowledge, this is the first study to report such an association. Interestingly, perfusion parameters –including HIR, a surrogate marker of collateral flow–[13] were not associated with END_i in our cohort, consistent with one smaller-scaled study of a similar population apart from a lower use of IVT.[14]

Longer thrombus and more proximal occlusion have been previously found to be the main predictors of lack of early post-IVT recanalization, both in minor[19] and non-minor stroke.[20-24] In turn, lack of early recanalization may be one pathophysiological link explaining the association observed here

between END_i and these variables.[7] Even though the precise mechanisms underlying END_i are still uncertain, one influential hypothesis is extension of 'symptomatic' ischemic tissue (*i.e.*, infarct core and/or penumbra) into the surrounding 'asymptomatic' tissue,[25,26] as a result of secondary hemodynamic, thrombotic and/or metabolic events in the context of persistent LVO.[5,25,26] Considering the apparent major role of hemodynamic or thrombotic factors, ensuring early recanalization with additional MT would appear a logical approach to prevent END_i.[8,27] However, the relatively small rate of END_i observed in our study may explain the lack of clear benefit derived from direct transfer for additional MT found in most observational studies in similar populations.[4,9,28-33] Interestingly, however, we recently reported that occlusion site is a strong modifier of the effect of additional MT on outcome, with additional MT being associated with higher odds of excellent outcome in M1 occlusions –*i.e.*, involving a high risk of post-IVT END_i–, but not in more distal occlusions –*i.e.*, with low END_i risk.[9]

END_i prediction score

Based on the above results, we derived and validated a clinical score intended to predict END_i after admission imaging, the aim being to assist physicians in assessing the risk of END_i, and in turn making a decision whether or not to immediately transfer the patient for additional MT. In the derivation cohort, patients with scores 0 and 1 –which includes two thirds of our sample– had very low rates of END_i (<7%), while patients with score 2 (22% of our sample) had a substantial risk (1 in 5), and those with scores 3 or 4 (15% of the sample) even larger risk –roughly 1 in 3. Importantly, our clinical score was externally validated, with very similar figures found in the validation cohort. Of note, the generalizability of our prediction score would if anything be strengthened by the differences in clinical-radiological variables present between the derivation and validation cohorts (Table 1).

Limitations

This study has several limitations. First, although it brings up important new data regarding the risk of END_i following IVT alone in minor stroke with LVO, our study does not directly inform whether bridging therapy is superior to IVT alone, even in the subgroups at highest risk of END_i. However, in line with the present results, another observational study from our large cohort suggests that bridging

therapy, as compared to IVT alone, may be beneficial only in patients with proximal LVO, *i.e.* those patients at higher risk of post-IVT END_i.[9] This will need to be confirmed in randomized trials. Second, 262 minor stroke patients with LVO treated with first-line bridging therapy were excluded from the derivation cohort (eFigure 1), which might have induced a selection bias. However >95% of these 262 patients were treated after 2015, and sensitivity analyses showed very similar results of prediction models regardless of whether patients were treated before or after this date. Third, clinical fluctuations before admission or on hospital arrival –either spontaneous or provoked by hemodynamic manoeuvers such as the head-up position[14]– may have relevance in END_i prediction,[14] but could not be retrospectively collected in a reliable way. Last, thrombus length was evaluated using two distinct imaging modalities. In our cohorts median thrombus length was however similar regardless of imaging modality, and furthermore the effect of thrombus length on incidence of END_i was quite similar across the two modalities.

Conclusions

In conclusion, our study documents a substantial rate of END_i in minor stroke with LVO treated with IVT, fuelling the current debate on whether bridging therapy should be carried out in this population. Second, we demonstrate that the odds of post-IVT END_i are strongly determined by occlusion site and thrombus length. Lastly, the straightforward score derived from these associations, and successfully validated in an independent cohort, affords good discriminative power for END_i prediction, which may eventually help clinicians for decision-making.

Sources of funding: none.

Disclosures: none.

Table 1. Characteristics of and comparison between the 2 cohorts.

	Derivation cohort N=729	Validation cohort N=347	*P* value
Patient history			
Age (years)	70 ±15	69 ±15	0.71
Male gender	335 (46)	190 (55)	<0.01
Hypertension	414 (57)	228 (66)	<0.01
Diabetes mellitus	112 (15)	59 (17)	0.49
Current smoking	131 (18)	60 (17)	0.79
Antiplatelets	212 (29)	120 (35)	0.07
Pre-IVT characteristics			
NIHSS score	3 (1-4)	3 (2-4)	0.32
Treatment after 2014	427 (59)	246 (71)	<0.01
Onset-to-IVT time (min)	162 (130-204)	175 (135-220)	<0.01
On-site endovascular facility	467 (64)	299 (86)	<0.01
Pre-IVT imaging			
MRI	657 (90)	229 (66)	<0.01
Occlusion site			<0.01
ICA-T/L	22 (3)	3 (1)	
Tandem	75 (10)	28 (8)	
Proximal M1	52 (7)	16 (5)	
Distal M1	155 (21)	44 (13)	
M2	395 (54)	244 (70)	
Basilar	30 (4)	12 (4)	
DWI-ASPECTS[a]	9 (8-9)	9 (8-10)	<0.01
Thrombus visible	621 (85)	324 (94)	<0.01
MRI	568 (87)	224 (98)	<0.01
CT/CTA	53 (74)	100 (85)	0.06
Thrombus length (mm)[b]	8.8 (6.0-11.9)	8.0 (6.0-10.0)	0.02
MRI[b]	8.9 (6.0-11.0)	8.0 (6.0-10.0)	0.07
CT/CTA[b]	8.6 (5.0-13.0)	7.0 (5.0-11.0)	0.63
END	96 (13)	44 (13)	0.84
END_i	88 (12)	38 (11)	0.63
END_i with rescue MT	49 (7)	17 (5)	0.25
END due to sICH	5 (1)	3 (1)	0.75
END due to other cause	3 (0)	3 (1)	0.35

a: patients with MRI only.

b: patients with visible thrombus only.

Abbreviations: CT indicates computerized tomography; CTA, CT angiography; DWI-ASPECTS, diffusion-weighted imaging Alberta Stroke program Early CT score; ICA-T/L, T or L intracranial internal carotid artery; END, early neurological deterioration; ENDi, END of presumed ischemic

origin; IVT, intravenous thrombolysis; M1; first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; sICH, symptomatic intracranial hemorrhage.

Continuous variables are presented as mean± standard deviation or median (interquartile range).

Table 2. Univariate relationships between baseline variables and END_i in the derivation cohort

	END_i n=88	**No-END[a] n=633**	***P* value**
Patient history			
Age (years)	69 ±15	70 ±15	0.25
Male gender	50 (57)	282 (45)	0.03
Hypertension	50 (58)	361 (57)	0.94
Diabetes mellitus	12 (14)	100 (16)	0.63
Current smoking	18 (21)	111 (18)	0.49
Antiplatelets	28 (32)	181 (29)	0.50
Pre-IVT characteristics			
NIHSS score	3.5 (2-5)	3 (1-4)	0.08
Treatment after 2014	55 (63)	367 (58)	0.42
Systolic BP (mmHg)[b]	154 (139-170)	150 (135-164)	0.08
Diastolic BP (mmHg)[b]	83 (75-90)	80 (70-90)	0.21
Onset-to-IVT time (min)	173 (129-215)	160 (130- 203)	0.23
On-site endovascular facility	62 (71)	401 (63)	0.19
Pre-IVT imaging			
MRI	80 (91)	569 (90)	0.77
Left hemispheric stroke[c]	40 (50)	303 (50)	0.95
Occlusion site			<0.001
ICA-T/L	12 (14)	10 (2)	
Tandem	17 (19)	58 (9)	
Proximal M1	10 (11)	42 (7)	
Distal M1	20 (23)	133 (21)	
M2	21 (24)	368 (58)	
Basilar	8 (9)	22 (4)	
DWI-ASPECTS[d]	9 (8-9)	9 (8-9)	0.66
Thrombus visible	76 (86)	538 (85)	0.74
Thrombus length (mm)[e]	11.5 (8.8-14.8)	8.3 (5.8-11.0)	<0.001
MRI[f]	11.0 (6.0-14.0)	8.3 (6.0-11.0)	<0.001
CT/CTA[g]	13.4 (10.4-15.7)	8.2 (5.0-11.3)	0.05
Tmax>6s volume (ml)[h]	41 (25-73)	34 (18-55)	0.23
Tmax>8s volume (ml)[h]	19 (8-35)	16 (6-31)	0.38
Tmax>10s volume (ml)[h]	10 (0-19)	9 (0-17)	0.67
HIR 10/6 (%)[h]	22 (0-32)	21 (0-37)	0.99
HIR 8/6 (%)[h]	47 (41-60)	47 (26-60)	0.53

a: 8 patients with END due to intracranial haemorrhage or clear alternative cause were excluded (see Results).

b: 23 patients had missing data (END_i, n=3; no-END, n=20).

c: 30 patients with basilar occlusion were excluded (END_i, n=8; no-END, n=22).

d: 649 patients with baseline MRI (END_i, n=80; no-END, n=569).

e: 107 patients without visible thrombus were excluded (END_i, n=12; no-END, n=95).

f: 69 patients with END_i and 492 without.

g: 7 patients with END_i and 46 without.

h: 186 patients with perfusion imaging (END_i, n=28; no-END, n=158).

Abbreviations: BP indicates blood pressure, CT, computerized tomography; CTA, CT angiography; DWI-ASPECTS, diffusion-weighted imaging Alberta Stroke program Early CT score; END_i, early neurological deterioration presumed of ischemic origin; HIR, hypoperfusion intensity ration; ICA-T/L, T or L intracranial internal carotid artery; IVT, intravenous thrombolysis; M1; first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MRI, magnetic resonance imaging; Tmax, time to maximum.

Continuous variables are presented as mean± standard deviation or median (interquartile range).

Table 3. Variables independently associated with END_i in multivariable logistic regression, including or excluding thrombus length (derivation cohort).

Model 1, excluding thrombus length[a] (n=721)		
	Adjusted OR (95%CI)	***P* value**
Occlusion site		<0.001
M2	Reference	
Distal M1	2.6 (1.4-5.0)	
Proximal M1	4.2 (1.8-9.4)	
Tandem	5.1 (2.6-10.3)	
ICA-T/L	21.0 (8.2-54.2)	
Basilar	6.4 (2.5-16.0)	
Model 2, including thrombus length[a] (n=614 with visible thrombus)		
	Adjusted OR (95%CI)	***P* value**
Occlusion site		<0.001
M2	Reference	
Distal M1	2.5 (1.2-5.1)	
Proximal M1	5.2 (2.1-13.1)	
Tandem	4.5 (2.1-9.7)	
ICA-T/L	16.0 (5.7-44.9)	
Basilar	7.2 (2.6-20.0)	
Thrombus length		0.002
<9mm	Reference	
≥9mm	3.2 (1.8-5.7)	

a: variables not retained in the model: NIHSS, sex, on-site endovascular facility, systolic blood pressure.

Abbreviations: CI indicates confidence interval; END_i, early neurological deterioration presumed of ischemic origin; ICA-T/L, T or L intracranial internal carotid artery; M1; first segment of middle cerebral artery; M2, second segment of middle cerebral artery; OR, odds ratio.

Figure legends

Figure 1. 3-month modified Rankin Scale scores according to (A) END_i status, and (B) rescue thrombectomy status in the END_i subgroup in the derivation cohort.

Modified Rankin score was not available for 37 patients (5 END_i and 32 no-END).

Abbreviations: END_i indicates early neurological deterioration presumed of ischemic origin.

Figure 2. Early neurological deterioration of presumed ischemic origin as a function of (A) occlusion site and (B) thrombus length in the derivation cohort.

A: END_i rates according to each occlusion site. Bars represent the 95% confidence intervals.

B: The regression curve estimates the probability of END_i according to thrombus length. The shaded area depicts the 95% confidence interval (logistic regression model).

Abbreviation: END_i indicates early neurological deterioration of presumed ischemic origin; ICA-T/L, intracranial internal carotid artery occlusion; M1: first segment of the middle cerebral artery; M2: second segment of the middle cerebral artery.

Figure 3. The END_i score for prediction of early neurological deterioration of presumed ischemic origin in patients with minor stroke due to intracranial large vessel occlusion. **A**: END_i score. **B**: Probability of END_i according to incremental points on the END_i Score applied to the derivation (gray bars) and validation (dashed bars) cohorts. Incremental points are presented in the x axis and probability of END_i in the y axis. Bars represent the 95% confidence intervals.

Abbreviations: END_i indicates early neurological deterioration presumed of ischemic origin; ICA-T/L, T or L intracranial internal carotid artery; M1; first segment of middle cerebral artery; M2, second segment of middle cerebral artery.

References

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2018;49(3):e46-e110.
2. Mazya MV, Cooray C, Lees KR, et al. Minor stroke due to large artery occlusion. When is intravenous thrombolysis not enough? Results from the SITS International Stroke Thrombolysis Register. *European Stroke Journal.* 2018;3(1):29-38.
3. Heldner MR, Jung S, Zubler C, et al. Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients. *J Neurol Neurosurg Psychiatry.* 2015;86(7):755-760.
4. Heldner MR, Chaloulos-Iakovidis P, Panos L, et al. Outcome of patients with large vessel occlusion in the anterior circulation and low NIHSS score. *J Neurol.* 2020;267(6):1651-1662.
5. Seners P, Baron JC. Revisiting 'progressive stroke': incidence, predictors, pathophysiology, and management of unexplained early neurological deterioration following acute ischemic stroke. *J Neurol.* 2018;265(1):216-225.
6. Seners P, Turc G, Oppenheim C, Baron JC. Incidence, causes and predictors of neurological deterioration occurring within 24 h following acute ischaemic stroke: a systematic review with pathophysiological implications. *J Neurol Neurosurg Psychiatry.* 2015;86(1):87-94.
7. Seners P, Turc G, Tisserand M, et al. Unexplained early neurological deterioration after intravenous thrombolysis: incidence, predictors, and associated factors. *Stroke.* 2014;45(7):2004-2009.
8. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO)- European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on

mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg.* 2019;11(6):535-538.

9. Seners P, Perrin C, Lapergue B, et al. Bridging Therapy or IV Thrombolysis in Minor Stroke with Large Vessel Occlusion. *Ann Neurol.* 2020;88(1):160-169.
10. Naggara O, Raymond J, Domingo Ayllon M, et al. T2* "susceptibility vessel sign" demonstrates clot location and length in acute ischemic stroke. *PLoS One.* 2013;8(10):e76727.
11. Rohan V, Baxa J, Tupy R, et al. Length of occlusion predicts recanalization and outcome after intravenous thrombolysis in middle cerebral artery stroke. *Stroke.* 2014;45(7):2010-2017.
12. Riedel CH, Jensen U, Rohr A, et al. Assessment of thrombus in acute middle cerebral artery occlusion using thin-slice nonenhanced Computed Tomography reconstructions. *Stroke.* 2010;41(8):1659-1664.
13. Olivot JM, Mlynash M, Inoue M, et al. Hypoperfusion intensity ratio predicts infarct progression and functional outcome in the DEFUSE 2 Cohort. *Stroke.* 2014;45(4):1018-1023.
14. Saleem Y, Nogueira RG, Rodrigues GM, et al. Acute Neurological Deterioration in Large Vessel Occlusions and Mild Symptoms Managed Medically. *Stroke.* 2020;51(5):1428-1434.
15. Kim JT, Heo SH, Yoon W, et al. Clinical outcomes of patients with acute minor stroke receiving rescue IA therapy following early neurological deterioration. *J Neurointerv Surg.* 2016;8(5):461-465.
16. Rajajee V, Kidwell C, Starkman S, et al. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. *Neurology.* 2006;67(6):980-984.
17. Kim JT, Park MS, Chang J, Lee JS, Choi KH, Cho KH. Proximal arterial occlusion in acute ischemic stroke with low NIHSS scores should not be considered as mild stroke. *PLoS One.* 2013;8(8):e70996.

18. Nacu A, Bringeland GH, Khanevski A, Thomassen L, Waje-Andreassen U, Naess H. Early neurological worsening in acute ischaemic stroke patients. *Acta Neurol Scand.* 2016;133(1):25-29.

19. Seners P, Delepierre J, Turc G, et al. Thrombus Length Predicts Lack of Post-Thrombolysis Early Recanalization in Minor Stroke With Large Vessel Occlusion. *Stroke.* 2019;50(3):761-764.

20. Seners P, Turc G, Naggara O, et al. Post-thrombolysis Recanalization in Stroke Referrals for Thrombectomy: Incidence, Predictors, and Prediction Scores. *Stroke* 2018;49:2975-2982.

21. Menon BK, Al-Ajlan FS, Najm M, et al. Association of Clinical, Imaging, and Thrombus Characteristics With Recanalization of Visible Intracranial Occlusion in Patients With Acute Ischemic Stroke. *JAMA.* 2018;320(10):1017-1026.

22. Seners P, Turc G, Maier B, Mas JL, Oppenheim C, Baron JC. Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. *Stroke.* 2016;47(9):2409-2412.

23. Kaesmacher J, Giarrusso M, Zibold F, et al. Rates and Quality of Preinterventional Reperfusion in Patients With Direct Access to Endovascular Treatment. *Stroke.* 2018. 2018;49(8):1924-1932.

24. Vanacker P, Heldner MR, Seiffge D, et al. ASTRAL-R score predicts non-recanalisation after intravenous thrombolysis in acute ischaemic stroke. *Thromb Haemost.* 2015;113(5):1121-1126.

25. Tisserand M, Seners P, Turc G, et al. Mechanisms of unexplained neurological deterioration after intravenous thrombolysis. *Stroke.* 2014;45(12):3527-3534.

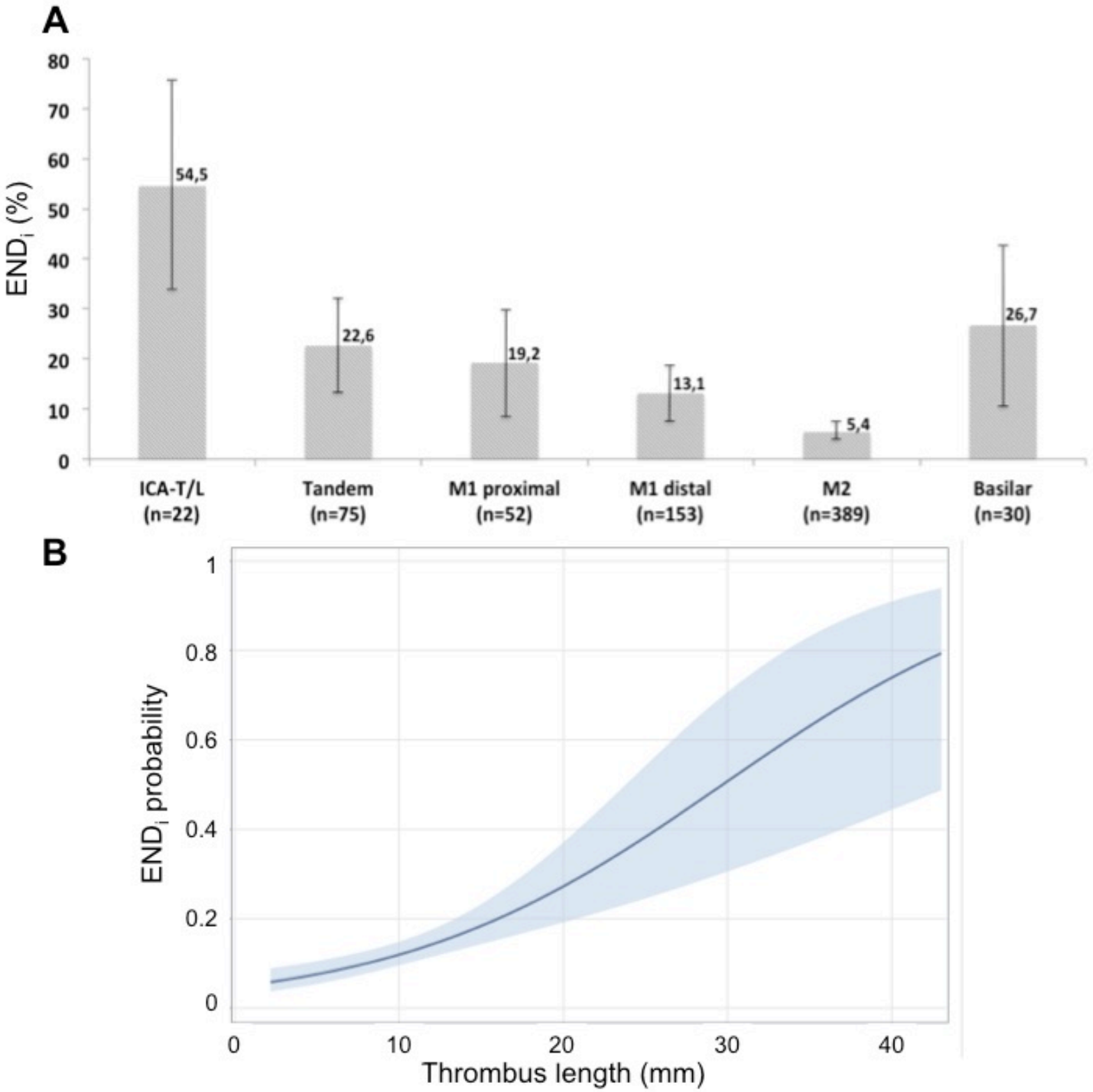
26. Fu J, Zhou Y, Li Q, et al. Perfusion Changes of Unexplained Early Neurological Deterioration After Reperfusion Therapy. *Transl Stroke Res.* 2020;11(2):195-203.

27. Dargazanli C, Consoli A, Gory B, et al. Is Reperfusion Useful in Ischaemic Stroke Patients Presenting with a Low National Institutes of Health Stroke Scale and a

Proximal Large Vessel Occlusion of the Anterior Circulation? *Cerebrovasc Dis.* 2017;43(5-6):305-312.

28. Goyal N, Tsivgoulis G, Malhotra K, et al. Medical Management vs Mechanical Thrombectomy for Mild Strokes: An International Multicenter Study and Systematic Review and Meta-analysis. *JAMA Neurol.* 2020;77:16–24.
29. Manno C, Disanto G, Bianco G, et al. Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms. *Neurology.* 2019;93(17):e1618-e1626.
30. Nagel S, Bouslama M, Krause LU, et al. Mechanical Thrombectomy in Patients With Milder Strokes and Large Vessel Occlusions. *Stroke.* 2018;49(10):2391-2397.
31. Dargazanli C, Arquizan C, Gory B, et al. Mechanical Thrombectomy for Minor and Mild Stroke Patients Harboring Large Vessel Occlusion in the Anterior Circulation: A Multicenter Cohort Study. *Stroke.* 2017;48(12):3274-3281.
32. Urra X, San Roman L, Gil F, et al. Medical and endovascular treatment of patients with large vessel occlusion presenting with mild symptoms: an observational multicenter study. *Cerebrovasc Dis.* 2014;38(6):418-424.
33. Sarraj A, Hassan A, Savitz SI, et al. Endovascular Thrombectomy for Mild Strokes: How Low Should We Go? *Stroke.* 2018;49:2398–2405.

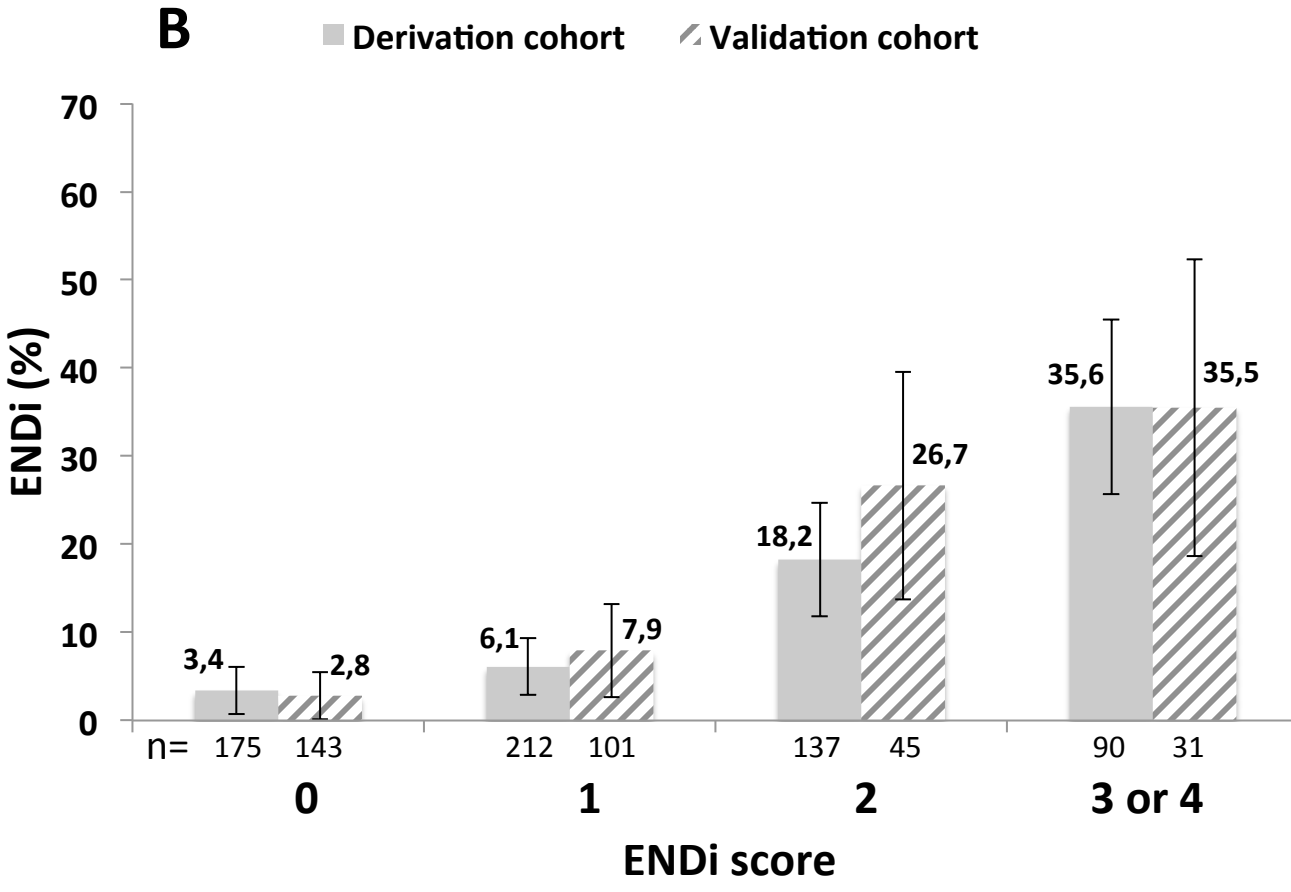

A
0
1
2
3
4
5
6
No-END (n=601)
54%
24%
11%
8%
2%
2%
END$_i$ (n=83)
17%
17%
17%
19%
13%
2%
14%
B
END$_i$ without rescue thrombectomy (n=37)
8%
8%
19%
19%
19%
5%
22%
END$_i$ with rescue thrombectomy (n=46)
24%
24%
15%
20%
9%
0%
9%


A
80
70
60
50
40
30
20
10
0
END$_i$ (%)
54,5
22,6
19,2
13,1
5,4
26,7
ICA-T/L (n=22)
Tandem (n=75)
M1 proximal (n=52)
M1 distal (n=153)
M2 (n=389)
Basilar (n=30)
B
1
0.8
0.6
0.4
0.2
0
END$_i$ probability
0
10
20
30
40
Thrombus length (mm)

A

Category	Points
Thrombus length	
<9mm	0
≥9mm	1
Occlusion site	+
M2	0
Distal M1	1
Proximal M1 or tandem or basilar	2
ICA-T/L	3

B



Supplemental materials

Supplemental Methods.

eTable 1. List of participating centers and dates of inclusion in the derivation and validation cohorts.

eTable 2. Comparison of END_i patients with or without rescue mechanical thrombectomy in the derivation cohort.

eTable 3. Variables independently associated with early neurological deterioration in multivariable logistic regression in sensitivity analysis including only patients treated before or since 2015 (derivation cohort).

eFigure 1. Study flowchart.

Supplemental Methods

Clinical data
The following variables were collected: age, gender, vascular risk factors, pre-stroke anti-thrombotic medication, presence of MT facility in the admission centre, time between symptom onset and start of IVT, blood pressure before IVT, NIHSS score on admission and at 24h, and 3-month modified Rankin Scale (mRS) score. Excellent functional outcome was defined as mRS<2. For patients receiving rescue MT we additionally collected time between (1) END_i and groin puncture and (2) groin puncture and reperfusion.

Radiological data
The M1 segment was defined as the first portion of the MCA up to the main bifurcation and was dichotomized as proximal or distal based on the MCA origin-to-clot interface distance (<10 and ≥10 mm, respectively).[7] Infarct core extent was evaluated using either the Alberta Stroke Program Early CT Score (ASPECTS) or diffusion-weighted imaging (DWI)-ASPECTS in patients with baseline CT or MRI, respectively. Whenever perfusion imaging was available, time-to-maximum (Tmax)>6s, >8s and >10s volumes were automatically segmented using the RAPID software (iSchemaView). Severity of hypoperfusion was assessed using the hypoperfusion intensity ratio (HIR), defined as the proportion of Tmax>6s volume with Tmax>10s (*i.e.,* HIR 10/6=[Tmax>10s volume / Tmax>6s volume] x100),[11] low HIR indicating milder hypoperfusion and better collaterals.[11] However, considering the low Tmax>10s volumes in this particular population of minor strokes, we also assessed the HIR using Tmax>8s instead of >10s (HIR 8/6).

Statistical analysis
Continuous variables were described as mean±standard deviation or median (interquartile range), as appropriate, and categorical variables as numbers and percentages. In the derivation cohort, we modeled the probability of a worse 3-month functional outcome in patients with and without END_i via an ordinal logistic regression, providing a common Odds Ratio (cOR) and its 95% confidence interval (95%CI) across the whole range of the mRS. The assumption of proportional odds was verified. To identify predictors of END_i, derive and validate a predictive score, the following steps were performed:

1. *Identification of independent predictors in the derivation cohort.* Univariable relationships between baseline variables and END_i were assessed using Student t test or Mann-Whitney U test for continuous variables and $\chi 2$ or Fisher's 'exact' test for categorical variables, as appropriate. Probability curves for the occurrence of END_i were created for continuous variables, based on univariable logistic regression. Considering the potential influence of the imaging modality (MRI *vs.* CT/CTA) on the determination of thrombus length, the thrombus length*imaging modality interaction to predict END_i was tested in a logistic regression model, and imaging modalities were merged for subsequent analyses considering the lack of interaction. To adjust for potential confounders, multivariable binary logistic regression analysis was subsequently conducted, with END_i 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 $P<0.05$ with the dependent variable. Two different models were developed, the first excluding thrombus length as this variable was not available for all patients, and the second including thrombus length. Covariates were assessed for collinearity and interaction effects. We then compared the discrimination afforded by the two predictive models using c-statistic (*i.e*. the area under the receiver operating characteristic curve) with 95%CI. Last, considering the potential selection bias due to exclusion of patients directly treated with bridging therapy mainly since 2015 (see Results), sensitivity analyses were performed on patients treated before and after 2015.

2. *Derivation of a score.* The above-mentioned model with the highest c-statistic was used to derive the END_i score, based on the magnitude of regression coefficients. Continuous variables independently associated with END_i were dichotomized using the Youden index to select a cutoff optimizing sensitivity and specificity for END_i prediction. Discrimination of the score to predict END_i 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. Discrimination of the score to predict END_i was again assessed using c-statistic with 95%CI. Calibration of the score was assessed by (i) comparing visually the predicted and observed risks of END_i across values of the END_i score in the validation cohort, and (ii) by estimating the Hosmer and Lemeshow test statistic (null hypothesis: the observed and predicted risks of END_i do not differ).

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

eTable 1. List of participating centers and dates of inclusion in the derivation and validation cohorts.

	Centre	Inclusion dates	Centre	Inclusion dates
Derivation cohort	Ste Anne (Paris)	2006-2018	Bourg-en-Bresse	2014-2016
	Pitié-Salpêtrière (Paris)	2006-2018	Maubeuge	2014-2017
	St Joseph (Paris)	2008-2018	Pontoise	2014-2018
	Reims	2009-2018	Marseille	2014-2018
	Lille	2010-2017	Narbonne	2014-2018
	Versailles	2010-2018	Rouen	2014-2018
	Lyon	2011-2015	Amiens	2015-2017
	St Etienne	2011-2017	Meaux	2015-2018
	Foch	2011-2018	Villefranche	2015-2018
	Nice	2012-2015	Bordeaux	2015-2018
	Toulon Ste Musse	2012-2016	Orsay	2015-2018
	Perpignan	2012-2018	Chambery	2016-2017
	Lens	2012-2018	Caen	2016-2017
	Valenciennes	2012-2018	Verdun	2016-2018
	Grenoble	2013-2015	Douai	2016-2018
	Vienne	2013-2016	Nancy	2016-2018
	St Antoine (Paris)	2013-2017	St Die des Vosges	2016-2018
	Calais	2013-2017	Mont St Martin	2016-2018
	Nantes	2013-2018	Sarrebourg	2016-2018
	Tours	2013-2018	Montpellier	2016-2018
	St Denis	2013-2018	Le Havre	2017-2018
	Rothschild (Paris)	2014-2017	Le Mans	2018-2018
	Toulon Ste Anne	2014-2017		
Validation cohort	Bern	2006-2019		
	Lausanne	2006-2019		
	Dijon	2010-2013 and 2016-2019		
	St Nazaire	2015-2018		
	Strasbourg	2015-2019		
	Orléans	2015-2019		
	Rennes	2015-2019		
	Genève	2016-2019		
	Brest	2009-2017		

eTable 2. Comparison of END_i patients with or without rescue mechanical thrombectomy in the derivation cohort.

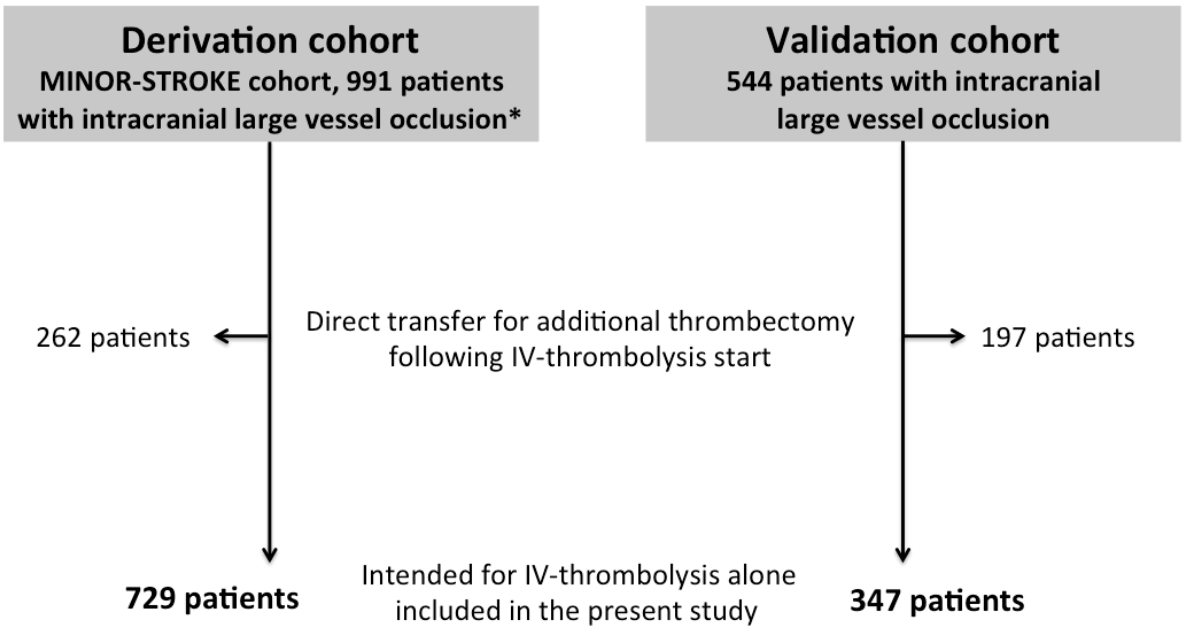
	END_i with rescue MT, n=49	**END_i without rescue MT, n=39**	***P* value**
Patient history			
Age (years)	68 ± 15	69 ± 15	0.69
Male gender	27 (55)	23 (59)	0.72
Hypertension	24 (50)	26 (67)	0.12
Diabetes mellitus	5 (10)	7 (18)	0.31
Current smoking	12 (25)	6 (15)	0.27
Antiplatelets	18 (38)	10 (26)	0.24
Pre-IVT characteristics			
NIHSS score	3 (2-4)	4 (2-5)	0.21
Treatment after 2014	38 (78)	17 (44)	**<0.01**
Onset-to-IVT time (min)	152 (126-204)	180 (149- 228)	0.09
On-site endovascular facility[a]	33 (67)	29 (74)	0.47
Pre-IVT imaging			
MRI	46 (94)	34 (87)	0.46
Occlusion site			0.54
ICA-T/L	5 (10)	7 (18)	
Tandem	11 (22)	6 (15)	
Proximal M1	7 (14)	3 (8)	
Distal M1	12 (25)	8 (21)	
M2	9 (18)	12 (31)	
Basilar	5 (10)	3 (8)	
DWI-ASPECTS[b]	9 (8-10)	9 (8-9)	0.11
Thrombus visible	44 (90)	32 (82)	0.29
Thrombus length (mm)[c]	10.0 (8.1-13.0)	13.1 (9.6-15.0)	0.06
ENDi characteristics			
NIHSS during END	10 (7-16)	12 (9-18)	0.18
IVT-to-END_i time (min)	80 (40-450)	420 (95-890)	**0.01**
END_i-to-puncture time (min)	95 (70-150)	NA	
On-site endovascular facility[a]	75 (50-119)	NA	
No on-site endovascular facility[d]	130 (110-184)	NA	
Puncture-to-reperfusion time (min)	67 (40-90)	NA	
mTICI 2b or 3	40 (81.6)	NA	

a: patients admitted in a stroke center with on site endovascular facility.
b: patients with baseline MRI only.
c: patients without visible thrombus were excluded.
d: these patients were transferred to an endovascular-capable centre for rescue thrombectomy.
Abbreviations: DWI-ASPECTS indicates diffusion-weighted imaging Alberta Stroke program Early CT score; END_i, early neurological deterioration presumed of ischemic origin; ICA-T/L, T or L intracranial internal carotid artery; IVT, intravenous thrombolysis; M1; first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MRI, magnetic resonance imaging; NA, not applicable. Continuous variables are presented as mean± standard deviation or median (interquartile range).

eTable 3. Variables independently associated with early neurological deterioration in multivariable logistic regression in sensitivity analysis including only patients treated before or since 2015 (derivation cohort).

Model 1, excluding thrombus length				
	Before 2015 (n=299)		**Since 2015 (n=422)**	
	Adjusted OR (95%CI)	***P* value**	**Adjusted OR (95%CI)**	***P* value**
Occlusion site		<0.001		<0.001
M2	Reference		Reference	
Distal M1	3.3 (0.9-12.1)		2.7 (1.3-5.7)	
Proximal M1	3.0 (0.5-17.4)		5.6 (2.1-14.4)	
Tandem	7.1 (1.9-26.7)		5.1 (2.2-11.9)	
ICA-T/L	36.7 (9.6-140.3)		27.8 (2.4-321.9)	
Basilar	11.0 (2.6-45.5)		6.0 (1.4-25.1)	
Model 2, including thrombus length				
	Before 2015 (n=249)		**Since 2015 (n=365)**	
	Adjusted OR (95%CI)	***P* value**	**Adjusted OR (95%CI)**	***P* value**
Occlusion site		0.001		0.001
M2	Reference		Reference	
Distal M1	3.0 (0.7-13.3)		2.3 (1.0-5.3)	
Proximal M1	3.8 (0.6-25.0)		6.6 (2.3-19.2)	
Tandem	4.0 (0.8-20.2)		4.3 (1.7-10.8)	
ICA-T/L	26.7 (5.8-122.4)		20.4 (1.7-250.8)	
Basilar	10.7 (2.1-53.6)		6.4 (1.4-29.6)	
Thrombus length, per each mm increase	1.10 (1.03-1.12)	0.009	1.07 (1.01-1.14)	0.035

eFigure 1. Study flowchart.



*81 patients from the MINOR-STROKE cohort with isolated cervical carotid occlusion (i.e., without associated large intracranial occlusion) were excluded.