Early neurological deterioration following thrombolysis for minor stroke with isolated internal carotid artery occlusion

Naouel Boulenoir, Guillaume Turc, Hilde Henon, Nadia Laksiri, François Mounier-Véhier, Isabelle Girard-Buttaz, Duc-Long Duong, Jérémie Papassin, Marion Yger, Aude Triquenot, et al.

Early neurological deterioration following thrombolysis for minor stroke with isolated internal carotid artery occlusion

Naouel Boulenoir,[1] MD; Guillaume Turc,[1] MD-PhD; Hilde Henon,[2] MD-PhD; Nadia Laksiri,[3] MD; François Mounier-Véhier,[4] MD; Isabelle Girard-Buttaz,[5] MD; Duc-Long Duong,[6] MD; Jérémie Papassin,[7,8] MD; Marion Yger,[9] MD; Aude Triquenot,[10] MD; Aïcha Lyoubi,[11] MD-MSc; Adrien Ter Schiphorst,[12] MD-MSc; Christian Denier,[13] MD-PhD; Jean-Claude Baron,[1] MD-ScD; Pierre Seners,[1] MD-PhD; on behalf of the MINOR-STROKE collaborators.

1: Neurology Department, GHU Paris psychiatrie et neurosciences, Sainte-Anne Hospital, Université de Paris, INSERM UMR 1266, FHU NeuroVasc, Paris, France.
2: Université de Lille, Inserm U1171, Degenerative and Vascular Cognitive Disorders, CHU Lille, Department of Neurology
3: Neurology Department, La Timone University Hospital, Marseille, France.
4: Neurology Department, Lens Hospital, France.
5: Neurology Department, Valenciennes Hospital, France.
6: Neurology Department, Versailles University Hospital, France.
7: Stroke Unit, Grenoble University Hospital, France.
8: Neurology Department, Chambery Hospital, France.
9: Neurology Department, Saint-Antoine Hospital, Paris, France.
10: Neurology Department, Rouen Hospital, France.
11: Neurology Department, Delafontaine hospital, St Denis, France.
12: Neurology Department, CHRU Gui de Chauliac, Montpellier, France.
13: Neurology Department, CHU Kremlin Bicêtre, France.

MINOR-STROKE collaborators: Wagih BEN HASSEN, Bertrand LAPERGUE, Chantal LAMY, Ludovic LUCAS, Frédéric PHILIPPEAU, Michael OBADIA, Michel PIOTIN, Omar BENNANI, Laura MECHTOUFF, Frédéric KLAPCZYNSKI, Olivier DETANTE, Caroline ARQUIZAN, Gioia MIONE, Denis SABLOT, Sébastien GAZZOLA, Séverine DEBIAIS, Serkan CAKMAK, Valer GRIGORAS, Ruben TAMAZYAN, Cécile PRETERRE, Charlotte ROSSO, Philippe NICLOT, Pierre GARNIER, Sébastien SOIZE, François LUN, Amélie TUFFAL, Marion BOULANGER, Sébastien GAZZOLA, Mathieu ZUBER, Fernando PICO, Frédéric CLARENÇON, Igor SIBON, Sonia ALAMOWITCH, Laurie FRATICELLI, Anne-Evelyne VALLET, Vincent COSTALAT, Catherine OPPENHEIM, Jean-Philippe COTTIER, Yves BERTHEZENE, Hubert DESAL, Pierre AGIUS, Omar BENNANI, Claire BOUTET, Nicolas BRICOUT, Didier LEYS, Mohamed CHBICHEB, Arnaud MALBRANQUE, Laurent SPELLE, Serge BRACARD, Mylène MASSON.

Correspondence: Pierre Seners, 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

Running title: Deterioration in isolated ICA occlusion

Word count: 3539.

Number of tables/figures: 3 / 2. Number of references: 25.

Key words: Cerebral ischemia; Thrombolysis; Thrombectomy.

ABSTRACT

Background: Better understanding the incidence, predictors and mechanisms of early neurological deterioration (END) following intravenous thrombolysis (IVT) for acute stroke with mild symptoms and isolated internal carotid artery occlusion (iICAo) may inform therapeutic decisions.

Methods: From a multicenter retrospective database we extracted all patients with both NIHSS<6 and iICAo (*i.e.* not involving the Willis circle) on admission imaging, intended for IVT alone. END was defined as ≥4 NIHSS points increase within 24hrs. END and no-END patients were compared for i) pre-treatment clinical and imaging variables, and ii) occurrence of intracranial occlusion, carotid recanalization and parenchymal hemorrhage on follow-up imaging.

Results: Seventy-four patients were included, among whom 22 (30%) patients experienced END. Among pre-treatment variables, supra-bulbar carotid occlusion was the only admission predictor of END following stepwise variable selection (OR=4.0; 95%CI 1.3-12.2; *P*=0.015). On follow-up imaging, there was no instance of parenchymal hemorrhage but an intracranial occlusion was now present in 76% *vs*. 0% of END and no-END patients, respectively (*P*<0.001), and there was a trend towards higher carotid recanalization rate in END patients (29% *vs*. 9%, *P*=0.07). As compared to no-END, END was strongly associated with poor 3-month outcome.

Conclusions: END is a frequent and highly deleterious event after IVT for minor stroke with iICAo, and is of thrombo-embolic origin in 3 out of 4 patients. The strong association with iICAo site – largely a function of underlying stroke etiology– may point to a different response of the thrombus to IVT. These findings suggest END may be preventable in this setting.

INTRODUCTION

Isolated cervical or intracranial internal carotid artery occlusion (iICAo), *i.e.*, not involving the circle of Willis, is found in ~5% of acute stroke patients admitted in an early time window [1]. Clinical severity is highly variable, in part as a function of collateral circulation [2]. The early clinical course of iICAo patients treated or not with reperfusion therapies has been reported in a few articles only [3-7], and remains poorly known. Following intravenous thrombolysis (IVT) –the recommended therapy for acute ischemic stroke in the early time window [8]–, a worrying 17% rate of early neurological deterioration (END) within the first 24 hours was recently reported in a multicentric cohort of iICAo patients with mild baseline symptoms [4].

Considering that END is strongly associated with poor 3-month functional outcome [4, 9], better understanding the mechanisms underlying END after acutely symptomatic iICAo may inform preventative decisions. Apart from symptomatic intracranial haemorrhage, two main underlying mechanisms, each with widely distinct therapeutic implications, may explain END in this context [10]: i) thrombo-embolic events, including distal artery-to-artery embolism and *in situ* extension of the original thrombus up the post-Willisian arteries, and ii) 'hemodynamic' failure, particularly in case of incomplete circle of Willis. For instance, while the former could be prevented using antithrombotics [3], the latter might be preventable via endovascular therapy (EVT) [5]. However, the predictors and mechanisms of END in this setting are largely unknown, and notably were not addressed in the above-mentioned study [4].

Here, we aimed to i) identify the incidence and predictors of END in a multicentric sample of iICAo patients with mild baseline symptoms treated with IVT, and ii) decipher the mechanisms of END in these patients.

METHODS

Study design and data sources

The MINOR-STROKE collaboration retrospectively collected the data from all consecutive acute stroke patients admitted to 45 French stroke centers between 2006 and 2018 who fulfilled the following criteria [11]: (1) baseline admission National Institutes of Health Stroke Scale (NIHSS) score ≤5; (2) large vessel occlusion on pre-treatment vascular imaging (internal carotid artery [ICA], first or second segment of middle cerebral artery [MCA], basilar artery), and (3) treated with IVT (alteplase only), with or without additional EVT. The present study focuses on patients with iICAo intended for IVT alone, including those who eventually received rescue EVT because of post-IVT END. The patients immediately intended for additional EVT following IVT (*i.e.*, bridging therapy) were excluded. iICAo was defined as cervical or intracranial internal carotid occlusion not involving the circle of Willis or the arteries distal to it.

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

Clinical data

The following variables were collected: age, gender, vascular risk factors, pre-stroke anti-thrombotic medication, blood pressure on admission, time between symptom onset and start of IVT, time between IVT and END, NIHSS score on admission and at 24h, 3-month modified Rankin Scale (mRS) score and stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment classification. Excellent functional outcome was defined as 3-month mRS<2 and good functional outcome as mRS<3.

Radiological data

All included patients underwent either MRI with MR-angiography or CT with CT-angiography before IVT start, and follow-up MRI/MRA or CT/CTA ~24hrs following admission. Additional MRI/MRA, CT/CTA or digital subtraction angiography was obtained in case of END. To ensure homogeneity in radiological evaluation, two stroke neurologists (NB and PS) reviewed independently all pre-IVT and

follow-up imaging blinded to clinical outcomes, including occurrence of END. Discrepancies were resolved by consensus.

On baseline imaging, the location of iICAo –dichotomized as bulbar and supra-bulbar, *i.e.*, within or upstream the ICA bulb, respectively– and the presence of anterior and posterior communicating arteries downstream the iICAo were collected. Perfusion imaging (CT- or MR-perfusion) was part of routine admission protocol in some centers. When available, the time-to-maximum (Tmax)>6s and >10s volumes were automatically segmented from perfusion imaging using Olea Sphere software, with manual correction whenever necessary [12]. 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=[Tmax>10s volume / Tmax>6s volume] X100) [13], low HIR indicating milder hypoperfusion.

On follow-up imaging (CT/CTA, MRI/MRA or digital subtraction angiography), the occurrence of (1) intracranial haemorrhage based on European Cooperative Acute Stroke Study imaging classification [14], (2) intracranial arterial occlusion ipsilateral to the initially occluded ICA, and (3) carotid recanalization defined as 2 or 3 on the Arterial Occlusive Lesion scale [15], were recorded. If several follow-up imaging sessions were performed, *e.g.* in case of END, we only considered the session closest in time to the occurrence of END. In this retrospective study plain CT was used as admission and/or follow-up parenchymal imaging in an important proportion of patients, and accordingly the topography of new infarcts was not systematically assessed.

Definition and classification of END

In this study, END refers to neurological deterioration with a NIHSS score increase ≥4 points within 24 hours after IVT [9]. For each END case, the presumed END mechanism was determined based on a careful review of baseline and follow-up clinical and radiological data. Apart from symptomatic intracranial haemorrhage, which was defined as END with parenchymal haemorrhage on follow-up imaging, END was categorized as thrombo-embolic or not. END of presumed thrombo-embolic origin was defined on follow-up vascular imaging as presence of new intracranial occlusion (middle, anterior or posterior cerebral arteries or anterior choroïdal artery) ipsilateral to the initially occluded

iICAo, and was sub-categorized as i) embolic (artery-to-artery embolism) if the new intracranial occlusion was not contiguous with the persistent carotid occlusion or if it was associated with ICA recanalization, ii) due to *in situ* extension of the carotid thrombus if in continuity, or iii) undetermined if it was not possible to determine whether the new intracranial occlusion was contiguous with the persistent ICA occlusion. If no new intracranial occlusion was identified, the END was considered of presumed non thrombo-embolic mechanism, which includes a hemodynamic origin.

Statistical analysis

Continuous variables were described as mean ± standard deviation or median (interquartile range [IQR]), as appropriate, and categorical variables as numbers and percentages. Univariable relationships between END and pre- or post-IVT variables 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. Regarding pre-IVT variables, to adjust for potential confounders, multivariable binary logistic regression analyses were subsequently conducted, with END as dependent variable. Pre-IVT 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. Statistical analyses were performed using SPSS 16.0 (SPSS, Inc). Two-tailed $P<0.05$ was considered statistically significant.

RESULTS

Study population

Out of 1072 patients included in the MINOR-STROKE cohort, a total of 74 IVT-treated patients with minor stroke and iICAo were included in the present study. Reasons for exclusion were no iICAo (n=992), lack of follow-up NIHSS score (n=1) or direct transfer for additional EVT (n=5). Mean age was 64 ±10 yrs, median NIHSS score was 3 (IQR 2-4) and median onset-to-IVT time was 170 mins (IQR 140-210). In 10 (14%) patients, iICAo was diagnosed on intracranial vascular imaging but the exact iICAo location (*i.e.*, bulbar or supra-bulbar) could not be determined because extracranial vascular imaging was not performed. In the remaining, iICAo was supra-bulbar in 27/64 (42%). After completion of etiological work-up, cause of stroke was large artery atherosclerosis, cardio-embolic, dissection and other/undetermined in 55%, 14%, 26% and 5% of patients, respectively. Perfusion imaging was available in 27 (36%) patients.

Incidence and characteristics of END

END occurred in 22 (29.7%, 95%CI: 19.3-40.1) patients. Median NIHSS score increase in END patients was 14 (IQR 11-17), and the timing of END was ≤2, 2-6, 6-12, and 12-24 hrs after IVT start in 55%, 14%, 14% and 18% of END patients, respectively. Following END, 14 (64%) patients were referred for rescue EVT, which was performed in 12 (2 patients had first-run angiography but no EVT performed because of clinical recovery following END).

Pre-IVT variables associated with END

The pre-IVT characteristics of patients with and without END and the results of the univariable analyses are presented in **Table 1**. END patients less frequently had diabetes and bulbar iICAo than no-END patients. Perfusion parameters did not significantly differ between the two groups, but the sub-sample was small. After stepwise variable selection, supra-bulbar iICAo was the sole variable retained in the model (OR=4.0; 95%CI: 1.3-12.2; *P*=0.015).

Post-IVT variables associated with END

The results of the univariable analyses for post-IVT variables for which an association with END were assessed are presented in **Table 2**. Occurrence of END was associated with non-atheromatous iICAo etiology (*i.e*., cardio-embolic, dissection or other/undetermined), with END rates of 5/41 (12%) and 17/33 (52%) for atheromatous *vs.* non-atheromatous iICAo, respectively. No instance of parenchymal haemorrhage was recorded in either group. Follow-up vascular imaging was performed more frequently and earlier in the END as compared to no-END group, and revealed the occurrence of an intracranial occlusion in 16 (76%) of END *vs*. 0 (0%) of no-END patients ($P<0.001$). Location of new-occurrence intracranial occlusion was intracranial carotid + first MCA segment, first MCA segment, second or more distal MCA segments, and anterior choroïdal artery in 5, 7, 3 and 1 patients, respectively. There was a strong trend towards higher ICA recanalization rate in END than no-END patients (29% *vs*. 9%, respectively, $P=0.07$). The rates of excellent and good functional outcomes were significantly lower in the END *vs.* no-END groups. However, ICA recanalization was not associated with 3-month outcome (mRS 0-1: 44% *vs.* 48% in recanalized and non-recanalized ICA patients, respectively, $P=0.86$; and mRS 0-2: 56% *vs*. 64%, respectively, $P=0.71$).

Presumed END mechanisms

The presumed END mechanisms are summarized in **Figure 1**, and the relevant clinical, imaging and rescue treatment data of the 22 END patients are detailed in **Table 3**. The END mechanism could not be determined in 1 patient without follow-up vascular imaging. Presumed END mechanism was thrombo-embolic in 16/21 (76%) patients with new-occurrence intracranial occlusion. Among these patients, END was sub-classified as embolic (artery-to-artery embolism) in 13 (81%) patients: 6 with new MCA occlusion associated with ICA recanalization and 7 with new MCA occlusion discontinuous from persistent ICA occlusion; and as *in situ* thrombus extension in one patient. In the remaining 2 patients, both with new-occurrence intracranial ICA + first MCA artery occlusion, the exact thrombo-embolic mechanism was unknown since it was not possible to determine whether the new intracranial occlusion was contiguous with the persistent cervical ICA occlusion.

Given the lack of intracranial occlusion on follow-up imaging, END was classified as non thrombo-embolic in 5/21 patients (24%). A hemodynamic origin appears likely in three of these patients

considering, in two patients, the lack of both anterior and posterior communicating arteries downstream the iICAo, and, in a third patient, the presence of an extensive severe hypoperfusion on post-END CT-perfusion, but remains uncertain for the two remaining patients. Blood pressure drops before END were not documented in any of these patients and newly appeared borderzone infarcts could not be documented as MRI both before and after END was performed in none. Three typical patients with END are shown in **Figure 2.**

DISCUSSION

Our aim in this multicenter study was to determine the incidence, predictors and mechanisms of post-IVT END in a sample of patients with acute mild stroke and iICAo. The study disclosed 3 key findings: (1) END affected 30% of patients and was strongly associated with poor 3-month outcome; (2) supra-bulbar iICAo site was the only independent predictor of END; and (3) a thrombo-embolic origin was the underlying mechanism in 3 out of 4 END patients, of which at least 81% was referable to artery-to-artery embolism.

Incidence of END and impact on outcome

We found that END affected 30% of patients with mild stroke and iICAo intended for IVT alone. Thus far, END in IVT-treated minor stroke patients with iICAo has been assessed in one previous study only [4], which reported an incidence of 17%, which is high yet not as high as the present study. This difference is likely explained by the exclusion of patients treated with rescue EVT (*i.e.*, performed because of END) in this previous study [4], inevitably implying an underestimated incidence of END.

Similar to all earlier studies on IVT-treated populations [4, 9, 16], END was strongly predictive of poor functional outcome, with only ~25% of END patients reaching 3-month functional independence. This further underlines the critical need to understand the predictors and underlying mechanisms of END in order to develop preventative strategies.

Predictors of END

Supra-bulbar ICA occlusion was the only independent predictor of END. This novel association likely mainly reflects the etiology underlying iICAo. Accordingly, stroke etiology, as established *post-hoc* following full etiological work-up, was strongly associated with END –non-atheromatous being at much higher END risk than atheromatous iICAo (52% *vs*. 12%, respectively). How could stroke etiology influence END risk in this population? We propose this observation may reflect a different response of the originally occluding carotid thrombus to IVT. Thus, on one hand the double association of END with both ICA recanalization and new intracranial occlusion (Table 2) might suggest that carotid thrombi that respond well to IVT might proceed to fragmentation causing new

intracranial occlusion, while, on the other hand, strokes due to large-artery atherosclerosis are known to be less prone to post-IVT recanalization as compared to other stroke subtypes [17, 18]. Also, it is possible that a fraction of the isolated ICA occlusions included in our study might in fact be chronic –particularly those of atheromatous origin–, and thereby less prone to post-IVT recanalization and fragmentation. The lack of association found between ICA recanalization and 3-month outcome (see Results) might suggest that post-IVT ICA recanalization is a dual edge sword in this setting: on one hand it might favor thrombus fragmentation, new intracranial occlusion and therefore END in some patients, while on the other hand it may improve cerebral perfusion and clinical recovery in other patients.

Mechanisms of END

To our knowledge, this is the first study to address END mechanisms in patients with iICAo. To determine presumed mechanism, we carefully analyzed for each END patient the available admission and follow-up imaging dataset. Interestingly, the predominant END mechanism turned out to be thrombo-embolic. This was evidenced by the presence of new-occurrence intracranial occlusion in 76% of END patients, as compared to 0% of no-END patients. A thrombo-embolic origin of END was reported in one previous study, which showed significantly more frequent thrombus extension in END than in no-END patients treated with IVT [19]. However, the vast majority of patients in this study had MCA occlusion, not iICAo. Two main underlying thrombo-embolic processes may lead to the occurrence of an intracranial occlusion in the setting of IVT-treated iICAo. The first is artery-to-artery embolism, which may result from fragmentation of the carotid thrombus involving either its entirety or its distal tail. This was found to be the primary mechanism in thrombo-embolic ENDs, occurring in 81% of thrombo-embolic END cases. The second thrombo-embolic mechanism, identified in one patient only, was *in situ* extension of the original carotid thrombus up the post-Willisian arteries. This secondary event may result from disrupted thrombosis pathways, such as increased coagulation activity and resistance to fibrinolysis, or activation of the physiological coagulation cascade because of blood stasis adjacent to the original thrombus, for instance as a result of poor collateral flow [20].

To our surprise, a presumed non thrombo-embolic, and therefore potentially hemodynamic, mechanism underlying END in our population was relatively rare, affecting at most 1 in 5 END patients only. Causes for such putative hemodynamic event could not be clearly determined in any of our patients, for instance blood pressure drops were not documented in any patient. 'Collateral failure', defined as insufficient endurance of collateral circulation to maintain cerebral perfusion pressure, has been proposed as a potential mechanism of END [21], yet its operational definition and exact underlying processes remain unclear [2, 10].

Importantly, none of the END patients in our cohort had symptomatic intracranial haemorrhage, consistent with previous findings in mild stroke [4].

Therapeutic implications: can END be prevented?

Given the apparent major role of thrombo-embolic factors in END, preventing distal embolization and *in situ* thrombus extension would appear as logical measures in the setting of IVT-treated iICAo. Three main approaches might be considered, namely i) avoiding IVT, ii) early administration of antithrombotics, and iii) direct referral for EVT. First, the effect of IVT on the thrombus in the setting of iICAo may be a double-edged sword: although IVT may prevent *in situ* thrombus extension and related ENDs, it could also cause thrombus fragmentation and subsequent distal embolism –the most frequent END mechanism based on the present study–, particularly in the event of ICA recanalization as observed here. Considering the very short half-life of alteplase, that it may favour embolic ENDs is further supported by the observation that most ENDs occurred within 2hrs from IVT start in our study. If true, this could mean that, at least in case of supra-bulbar iICAo, withholding IVT might prevent END. As a caveat, this scenario cannot be inferred from our dataset as a control group (*i.e.,* non IVT-treated iICAo) was not available. Although IVT likely is beneficial in acute minor strokes with intracranial occlusions [22], further studies are warranted specifically regarding minor strokes with iICAo. Note that in the observational ICARO study [23], which reported better outcomes in IVT- as compared to non IVT-treated patients with ICA occlusion, the proportion of patients with iICAo is unknown as occurrence of tandem ICA + MCA occlusions is not presented. Second, early post-IVT antithrombotic administration may be an attractive option to prevent thrombo-embolic ENDs. Regarding antiplatelet therapy, a *post hoc* analysis of the ARTIS trial, a randomized trial comparing

ultra-early (within 90min of IVT start) addition of aspirin after IVT *vs.* IVT alone in an unselected acute stroke population, found that aspirin increased the risk of END due to intracranial hemorrhage, and had no effect on incidence of non-hemorrhagic END [24]. However, this approach may still be of interest in populations at high risk of post-IVT thrombo-embolic END and low risk of intracranial hemorrhage, such as supra-bulbar iICAo with mild symptoms, and should be further tested. As another antithrombotic approach, a recent observational study in patients not candidates for IVT suggested that, as compared to antiplatelet therapy, anticoagulation was associated with lower 7-day END rate in iICAo patients admitted within 24hrs from onset (7% *vs.* 39%, respectively, *P*=0.03) [3]. However, in the setting of IVT, the considerably higher risk of intracranial hemorrhage strongly limits such therapy. Last, regarding direct referral for EVT, two recently published case series showed that immediate EVT, which includes acute angioplasty and stenting, is feasible in the setting of iICAo [5, 6] and afforded high rates of successful recanalization, but was also associated with a high rate (22%) of distal embolism [5]. However, the vast majority of iICAo patients in these studies had high baseline NIHSS scores [5, 6], and it may not be warranted to extrapolate their findings to our population. Randomized trials are needed to test these different strategies.

Regarding hemodynamic ENDs, apart from routine physiological measures to maintain collateral flow [25], the most logical measures to efficiently prevent hemodynamic failure in iICAo would appear to be direct EVT, including angioplasty-stenting, and collateral enhancing strategies such as induced hypertension, lying flat head position or volume expansion [25].

Limitations

Our study has several limitations. First, despite the multicenter design, the overall sample was relatively small, thereby limiting the statistical analysis. This can be explained by the relative rarity of iICAo in the acute stroke setting [1]. Second, considering the retrospective nature of the study, baseline and follow-up imaging was not standardized. Consequently, only few patients had baseline perfusion imaging, and the lack of prognostic value of perfusion parameters found here should be interpreted cautiously. Third, due to the intrinsic limitations of non-invasive vascular imaging, some patients with baseline severe carotid stenosis may have been misclassified as iICAo, in particular for those 10 patients without extracranial vascular imaging. Fourth, transcranial Doppler continuous-

monitoring, which may have helped to determine the exact END mechanism, was not available in the participating centres. Fifth, as our study focused on iICAo with mild baseline symptoms treated with IVT, the results cannot be generalized to iICAo patients with more severe symptoms and/or not treated with IVT. Last, as a control group -*i.e*., acute iICAo with mild symptoms not treated with IVT- was not available, it is unknown whether the clinical course described here was modified by IVT. Further research is warranted.

CONCLUSIONS

END is a frequent and highly deleterious event after IVT for minor stroke with iICAo. This study identified a thrombo-embolic origin as mechanism underlying 3/4th of the ENDs, with artery-to-artery embolism involved in the vast majority of these patients. The strong association with iICAo site, which reflects underlying stroke etiology, might reflect a different thrombus response to thrombolysis. Our findings may have potential implications regarding prevention of END in this setting. However, further studies are needed at this stage to confirm and expand our findings.

Acknowledgements: none.

Source of funding: none.

Conflict of interest: the authors report no competing interest concerning this manuscript.

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

Figure :

Figure 1: Presumed END mechanisms

END of presumed thrombo-embolic origin was defined on follow-up vascular imaging as presence of new intracranial occlusion ipsilateral to the initially occluded iICAo, and was sub-categorized as i) embolic (artery-to-artery embolism) if the new intracranial occlusion was not contiguous with the persistent carotid occlusion or if it was associated with ICA recanalization, ii) due to *in situ* extension of the carotid thrombus if in continuity, or iii) undetermined if it was not possible to determine whether the new intracranial occlusion was contiguous with the persistent ICA occlusion. If no new intracranial occlusion was identified, the END was considered of presumed non thrombo-embolic mechanism, which includes a hemodynamic origin. See Table 3 for details and Figure 2 for illustrative cases.

Figure 2: Illustrative END cases.

Patient 1: embolic END (patient#7 in Table 3): Forty-seven years old patient with mild right brachio-facial paresis and dysphasia (baseline NIHSS 4). *Baseline imaging:* CT and CTA obtained 240min after stroke onset showed no abnormality on plain CT, and a left supra-bulbar ICA occlusion (arrowhead) without intracranial occlusion. IVT was started 260min after stroke onset and the patient experienced a severe END 8h following IVT, with occurrence of right hemiplegia and severe dysphasia (NIHSS 20). *Follow-up imaging:* MRI performed 1hr following END showed a large DWI lesion in the MCA territory and an occlusion of the intracranial ICA and M1 segment with a long thrombus visible on T2* (arrows). First angiographic run confirmed the intracranial ICA + M1 occlusion, which was not contiguous with the persistent supra-bulbar occlusion (not shown). Mechanical thrombectomy (aspiration catheter) was performed with successful intracranial reperfusion reached 145min following END (modified thrombolysis in cerebral infarction score 2b). NIHSS at 24hr was 11 and 3-month mRS was 3.

Patient 2: embolic END (patient#1 in Table 3): Fifty-six years old patient with mild right brachio-facial paresis and dysphasia (NIHSS 5). *Baseline imaging:* MRI and MRA obtained 110min after stroke onset showed a small DWI lesion in the left cortical MCA territory, and a left supra-bulbar ICA occlusion (arrowhead) without intracranial occlusion. IVT was started 130min after stroke onset and the patient experienced a severe END 1h following IVT, with right hemiplegia and severe dysphasia (NIHSS 22). *Follow-up imaging:* CT performed 30min following END was unremarkable save for left hyperdense MCA sign (arrow), and the first intracranial run of angiography showed ICA recanalization and a left M1 occlusion (arrow). Mechanical thrombectomy was

performed, with successful reperfusion reached 113min following END (modified thrombolysis in cerebral infarction score 3). NIHSS at 24hr and 3-month mRS were 0.

Patient 3: Non thrombo-embolic –likely hemodynamic– END (patient #18 in Table 3): Forty-four years old patient with a fluctuating mild right hemiparesis and dysarthria (admission NIHSS=5). *Baseline imaging:* MRI and MRA obtained 210min after stroke onset showed small DWI lesions in the borderzone of the left ICA territory, together with an extensive area of severe hypoperfusion (Tmax>6s [yellow]=108ml, Tmax>10s [orange]=17ml; HIR=16%) and a left ICA occlusion with a trickle of flow in the left MCA (arrow). IVT was started 230min after stroke onset and an additional CTA was performed immediately after IVT start showing a left supra-bulbar ICA occlusion (arrowhead) without intracranial occlusion. The patient experienced severe END 45mins following IVT start, with right hemiplegia and severe dysphasia (NIHSS=17). *Follow-up imaging:* plain CT obtained 30min following END showed no hemorrhage (not shown) and first angiographic run following left common carotid artery injection showed persistent ICA occlusion (arrowheads) without intracranial occlusion. The left MCA was poorly reconstituted (arrows) through collaterals arising from the external carotid artery.

References:

[1]. Turc G, Maier B, Naggara O*, et al.* Clinical Scales Do Not Reliably Identify Acute Ischemic Stroke Patients With Large-Artery Occlusion. *Stroke*. 2016 **47:** 1466-1472.

[2]. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol*. 2011 **10:** 909-921.

[3]. Damania D, Kung NT, Jain M*, et al.* Factors associated with recurrent stroke and recanalization in patients presenting with isolated symptomatic carotid occlusion. *Eur J Neurol*. 2016 **23:** 127-132.

[4]. 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.

[5]. Jadhav A, Panczykowski D, Jumaa M*, et al.* Angioplasty and stenting for symptomatic extracranial non-tandem internal carotid artery occlusion. *J Neurointerv Surg*. 2018 **10:** 1155-1160.

[6]. de Castro-Afonso LH, Nakiri GS, Moretti Monsignore L*, et al.* Endovascular Reperfusion for Acute Isolated Cervical Carotid Occlusions: The Concept of "Hemodynamic Thrombectomy". *Interv Neurol*. 2020 **8:** 27-37.

[7]. Gliem M, Lee JI, Barckhan A, Turowski B, Hartung HP, Jander S. Outcome and Treatment Effects in Stroke Associated with Acute Cervical ICA Occlusion. *PLoS One*. 2017 **12:** e0170247.

[8]. 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:** e46-e110.

[9]. 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:** 87-94.

[10]. 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:** 216-225.

[11]. Seners P, Perrin C, Lapergue B*, et al.* Bridging therapy or IV-thrombolysis in minor stroke with large vessel occlusion. *Ann Neurol*. 2020 **88:**160-169.

[12]. Olea-Medical. https://www.olea-medical.com/en/. 2020.

[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:** 1018-1023.

[14]. Hacke W, Kaste M, Fieschi C*, et al.* Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995 **274:** 1017-1025.

[15]. Zaidat OO, Yoo AJ, Khatri P*, et al.* Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013 **44:** 2650-2663.

[16]. Seners P, Turc G, Tisserand M*, et al.* Unexplained early neurological deterioration after intravenous thrombolysis: incidence, predictors, and associated factors. *Stroke*. 2014 **45:** 2004-2009.

[17]. Kim YS, Garami Z, Mikulik R, Molina CA, Alexandrov AV. Early recanalization rates and clinical outcomes in patients with tandem internal carotid artery/middle cerebral artery occlusion and isolated middle cerebral artery occlusion. *Stroke*. 2005 **36:** 869-871.

[18]. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabin J. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke*. 2004 **35:** 486-490.

[19]. Seners P, Hurford R, Tisserand M*, et al.* Is Unexplained Early Neurological Deterioration After Intravenous Thrombolysis Associated With Thrombus Extension? *Stroke*. 2017 **48:** 348-352.

[20]. Qazi EM, Sohn SI, Mishra S*, et al.* Thrombus Characteristics Are Related to Collaterals and Angioarchitecture in Acute Stroke. *Can J Neurol Sci*. 2015 **42:** 381-388.

[21]. Liebeskind DS, Kim D, Starkman S*, et al.* Collateral failure? Late mechanical thrombectomy after failed intravenous thrombolysis. *J Neuroimaging*. 2010 **20:** 78-82.

[22]. Tsivgoulis G, Goyal N, Katsanos AH*, et al.* Intravenous thrombolysis for large vessel or distal occlusions presenting with mild stroke severity. *Eur J Neurol*. 2020 **27:** 1039-1047.

[23]. Paciaroni M, Balucani C, Agnelli G*, et al.* Systemic thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion: the ICARO study. *Stroke*. 2012 **43:** 125-130.

[24]. Zinkstok SM, Beenen LF, Majoie CB, Marquering HA, de Haan RJ, Roos YB. Early deterioration after thrombolysis plus aspirin in acute stroke: a post hoc analysis of the Antiplatelet Therapy in Combination with Recombinant t-PA Thrombolysis in Ischemic Stroke trial. *Stroke*. 2014 **45:** 3080-3082.

[25]. Bang OY, Goyal M, Liebeskind DS. Collateral Circulation in Ischemic Stroke: Assessment Tools and Therapeutic Strategies. *Stroke*. 2015 **46:** 3302-3309.

Table 1. Univariate relationships between pre-IVT variables and END

	END n=22	**No-END n=52**	***P* value**
Patient history			
Age (years)	62 (54-71)	64 (54-74)	0.97
Male gender	16 (73)	40 (77)	0.70
Hypertension	13 (59)	23 (44)	0.24
Diabetes mellitus	0 (0)	11 (21)	**0.03**
Current smoking	7 (32)	18 (35)	0.77
Antiplatelets	6 (27)	14 (27)	0.98
Pre-IVT characteristics			
NIHSS score	3 (2-5)	3 (1-4)	0.17
Systolic blood pressure (mmHg)†	145 (135-163)	153 (140-160)	0.26
Diastolic blood pressure (mmHg)†	87 (77-95)	84 (79-93)	0.72
Onset-to-IVT time (min)	189 (133-225)	160 (141-207)	0.36
Pre-IVT imaging			
iICAo site‡			**0.01**
Bulbar	7 (35)	30 (68)	
Supra-bulbar	13 (65)	14 (32)	
Completeness of Willis circle§			0.99
No communicating artery	3 (14)	7 (14)	
One communicating artery	10 (45)	24 (46)	
Two communicating arteries	9 (41)	21 (40)	
Perfusion parameters¶			
Tmax>6s volume (ml)	14 (3-63)	25 (3-63)	0.94
Tmax>10s volume (ml)	5 (1-6)	2 (0-14)	0.86
HIR (%)	18 (7-24)	9 (0-27)	0.74

†: available for 72 patients (22 END and 50 no-END patients).

‡: available for 64 patients (20 END and 44 no-END patients). For 10 patients, the precise ICA occlusion site could not be determined because extracranial vascular imaging was not performed.

§: the presence of communicating arteries was evaluated for the iICAo side only.

¶: available for 27 patients (9 END and 18 no-END).

Abbreviations: END indicates early neurological deterioration; IVT, intravenous thrombolysis; iICAo, isolated internal carotid artery occlusion; Tmax, time-to-maximum volume; HIR, hypoperfusion intensity ratio.

Table 2. Univariable relationships between post-IVT variables and END

	END n=22	**No-END n=52**	***P* value**
Stroke etiology			**<0.001**
Atherosclerosis	5 (23)	36 (69)	
Other†	17 (77)	16 (31)	
Follow-up imaging‡			
Baseline to f/u imaging time (hours)	6 (2-21)	25 (21-28)	**<0.001**
Parenchymal hemorrhage	0 (0)	0 (0)	NA
Intracranial occlusion occurrence§	16 (76)	0 (0)	**<0.001**
ICA recanalization§	6 (29)	3 (9)	0.07
3-month outcome¶			
mRS<2	4 (20)	35 (71)	**<0.001**
mRS<3	5 (25)	43 (88)	**<0.001**

†: Cardio-embolic, dissection, other or undetermined.

‡: If several follow-up imaging were performed, *e.g.* in case of END, we only considered the closest in time to the occurrence of END.

§: A follow-up vascular imaging was performed in 55 patients (21 END and 34 no-END).

¶: Available for 69 patients (20 END and 49 no-END).

Abbreviations: END indicates early neurological deterioration; ICA, internal carotid artery; IVT, intravenous thrombolysis; mRS, modified Rankin scale.

Table 3. Clinical and imaging data of the 22 END patients (listed in order of presumed mechanism).

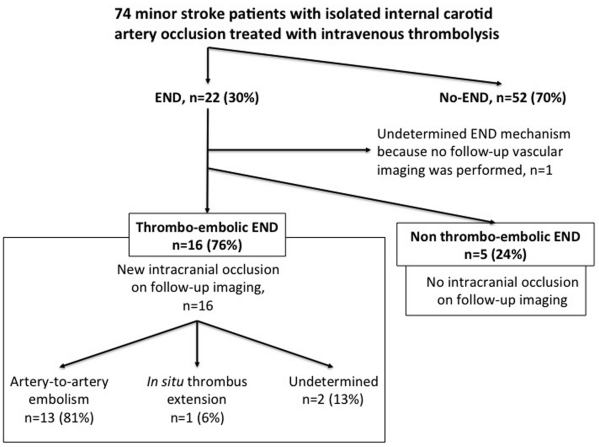
Patient No. Age, sex	Baseline imaging	Initial/ END NIHSS	Onset to IVT time, min	Timing of END†, h	Post-END imaging†	Stroke etiology	END presumed mechanism	Acute treatment following END	24h NIHSS /3-month mRS
1, 56/M	Supra-bulbar iICAo ACoA+/PCoA- No perfusion imaging	5 / 22	130	1	M1 occlusion ICA recanalization	CE	Embolic	MT (aspiration); mTICI 3 reached 113min following END	0 / 0
2, 95/F	Supra-bulbar iICAo ACoA+/PCoA- Tmax>6s=14ml Tmax>10s=6ml HIR=40%	1 / 18	55	6	M1 occlusion ICA recanalization	CE	Embolic	None	18 / 5
3, 85/M	Unknown iICAo site‡ ACoA+/PCoA- No perfusion imaging	3 / 20	225	1	M1 occlusion ICA recanalization	CE	Embolic	MT (stentriever); mTICI 3 reached 206min following END	4 / 1
4, 87/F	Bulbar iICAo ACoA-/PCoA+ Tmax>6s=11ml Tmax>10s=0ml HIR=0%	2 / 20	200	1	Intracranial ICA + M1 occlusion Bulbar ICA recanalization	LAA	Embolic	MT (stentriever); mTICI 3 reached 195min following END	21 / 6
5, 66/M	Bulbar iICAo ACoA+/PCoA- Tmax>6s=180ml Tmax>10s=35ml HIR=19%	5 / 20	220	1.5	Intracranial ICA + M1 occlusion Bulbar ICA recanalization	LAA	Embolic	MT (aspiration+stentriever) and bulbar ICA angioplasty/stenting; mTICI 2b reached 130min following END	NA / 4
6, 64/F	Bulbar iICAo ACoA+/PCoA+ No perfusion imaging	2 / 13	240	0.5	M1 occlusion ICA recanalization	LAA	Embolic	MT (aspiration); mTICI 2b reached 357min following END	13 / 3
7, 47/M	Supra-bulbar iICAo ACoA+/PCoA+ Tmax>6s=2ml Tmax>10s=1ml HIR=41%	4 / 20	260	8	Intracranial ICA + M1 occlusion Persistent cervical ICA occlusion	D	Embolic	MT (aspiration); mTICI 2b reached 145min following END.	11 / 3
8, 54/M	Supra-bulbar iICAo ACoA+/PCoA+ Tmax>6s=23ml Tmax>10s=4ml HIR=18%	3 / 13	133	22	M2 and P2 occlusion§ Persistent ICA occlusion	D	Embolic	None	11 / 3
9, 58/M	Supra-bulbar iICAo ACoA+/PCoA- No perfusion imaging	3 / 21	240	13	M1 occlusion Persistent ICA occlusion	O	Embolic	None	21 / 4
10, 46/M	Supra-bulbar iICAo ACoA+/PCoA+ Tmax>6s=3ml Tmax>10s=1ml HIR=24%	3 / 15	180	24	M2 occlusion Persistent ICA occlusion	D	Embolic	None	15 / 3
11, 54/M	Supra-bulbar iICAo ACoA+/PCoA- Tmax>6s=0ml Tmax>10s=0ml HIR=0%	1 / 12	190	7	M1 occlusion Persistent ICA occlusion	D	Embolic	MT (stentriever); mTICI 2b reached 184min following END	11 / 2

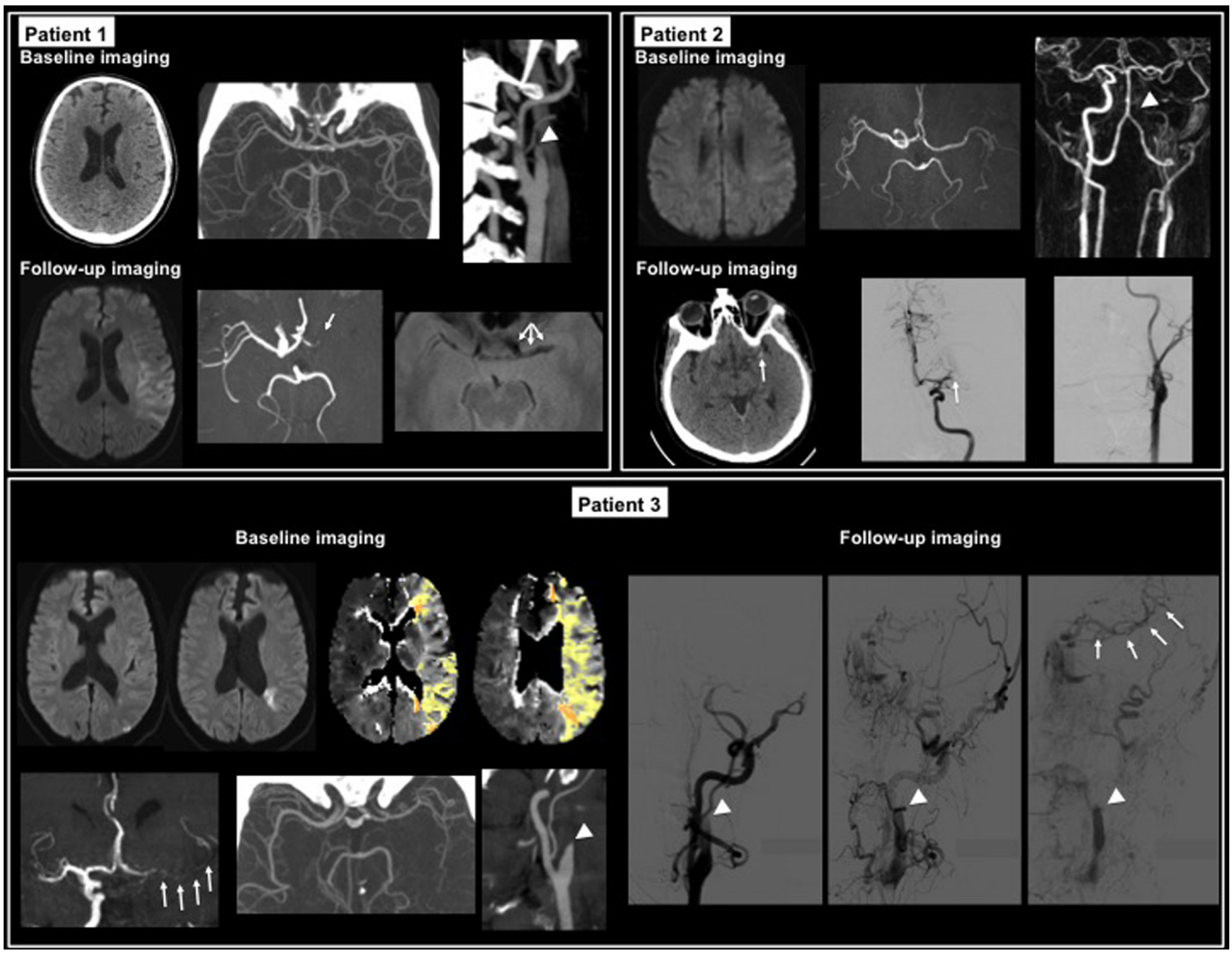
Patient No. Age, sex	Baseline imaging	Initial/ END NIHSS	Onset to IVT time, min	Timing of END†, h	Post-END imaging†	Stroke etiology	END presumed mechanism	Acute treatment following END	24h NIHSS /3-month mRS
12, 67/M	Bulbar iICAo ACoA+/PCoA+ No perfusion imaging	5 / 17	205	0.5	M1 occlusion Persistent ICA occlusion	LAA	Embolic	MT (aspiration+stentriever); mTICI 2a reached 264min following END and ICA angioplasty/stenting	17 / 6
13, 71/M	Bulbar iICAo ACoA+/PCoA+ No perfusion imaging	5 / 24	100	2	M2 and M3 occlusions Persistent ICA occlusion	CE	Embolic	No MT (distal occlusions), ICA angioplasty/stenting	17 / 4
14, 70/M	Supra-bulbar iICAo ACoA+/PCoA+ No perfusion imaging	0 / 15	188	0.5	Anterior choroïdal artery occlusion Persistent ICA oclusion	CE	*In situ* thrombus extension¶	None	8 / NA
15, 85/M	Bulbar iICAo ACoA-/PCoA- Tmax>6s=87ml Tmax>10s=6ml HIR=7%	5 / 24	131	23	Intracranial ICA + M1 occlusion Persistent cervical ICA occlusion	LAA	Thrombo-embolic (undetermined)††	None	24 / 6
16, 50/F	Supra-bulbar iICAo ACoA+/PCoA+ No perfusion imaging	5 / 15	90	2	Intracranial ICA + M1 occlusion Persistent cervical ICA occlusion	O	Thrombo-embolic (undetermined)††	None	18 / 3
17, 44/M	Supra-bulbar iICAo ACoA-/PCoA- Tmax>6s=108ml Tmax>10s=17ml HIR=16%	5 / 17	230	1	No intracranial occlusion Persistent ICA occlusion	D	Non thrombo-embolic	Aspiration of ICA clot. Persistent iICAo at end of procedure.	15 / 3
18, 59/F	Supra-bulbar iICAo ACoA-/PCoA- No perfusion imaging	3 / 12	180	1	No intracranial occlusion Persistent ICA occlusion	D	Non thrombo-embolic	None (angiography performed but no endovascular procedure because of clinical recovery)	1 / 0
19, 87/F	Bulbar iICAo ACoA+/PCoA- No perfusion imaging	3 / 7	230	10	No intracranial occlusion Persistent ICA occlusion§§	CE	Non thrombo-embolic	Aspiration of ICA clot allowing recanalization.	7 / NA
20, 61/M	Supra-bulbar iICAo ACoA+/PCoA- No perfusion imaging	4 / 19	150	1	No intracranial occlusion Persistent ICA occlusion	D	Non thrombo-embolic	Angioplasty/stenting of ICA allowing recanalization.	10 / 3
21, 60/M	Supra-bulbar iICAo ACoA+/PCoA+ No perfusion imaging	2 / 11	180	3	No intracranial occlusion Persistent ICA occlusion	D	Non thrombo-embolic	None (angiography performed but no endovascular procedure because of clinical recovery)	4 / 0
22, 66/F	Unknown iICAo site‡ ACoA+/PCoA- No perfusion	4 / 15	200	2.5	No follow-up vascular imaging	CE	Undetermined‡‡	None	15 / 4

†Following intravenous thrombolysis start.
‡: Extracranial vascular imaging was not performed.
§: The posterior cerebral artery arose from the ICA.
¶: On baseline imaging this patient had a supra-bulbar iICAo with clot visible up to the distal end of ICA on susceptibility weighted imaging upstream the anterior choroïdal artery origin. MRI performed following END showed distal extension of the ICA thrombus on susceptibility weighted imaging now occluding the anterior choroïdal artery, with corresponding territory infarct.

††: The exact thrombo-embolic mechanism (*i.e.*, artery-to-artery embolism *vs. in situ* thrombus extension) is unknown in these patients since it is not possible to determine whether the new intracranial ICA + first MCA segment occlusion was contiguous with the persistent cervical ICA occlusion.
‡‡: The END mechanism (thrombo-embolic vs. non thrombo-embolic) is undetermined because of the lack of follow-up vascular imaging.
§§: A CT-perfusion was performed following END, showing a large severe hypoperfusion (Tmax>6s=140ml, Tmax>10s=3ml, HIR=2%).

Abbreviations: ACoA indicates anterior communicating artery; CE, cardio-embolic; D, dissection; END, early neurological deterioration; HIR, hypoperfusion intensity ratio; iICAo, isolated internal carotid occlusion; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; MCA, middle cerebral artery; mRS, modified Rankin scale; MT, mechanical thrombectomy; mTICI, modified thrombolysis in cerebral infarction scale; mRS, modified Rankin scale; NA, not available; O: other or undetermined; PCoA, posterior communicating artery.


74 minor stroke patients with isolated internal carotid artery occlusion treated with intravenous thrombolysis
END, n=22 (30%)
No-END, n=52 (70%)
Undetermined END mechanism because no follow-up vascular imaging was performed, n=1
Thrombo-embolic END n=16 (76%)
Non thrombo-embolic END n=5 (24%)
No intracranial occlusion on follow-up imaging
New intracranial occlusion on follow-up imaging, n=16
Artery-to-artery embolism n=13 (81%)
In situ thrombus extension n=1 (6%)
Undetermined n=2 (13%)


Patient 1
Baseline imaging
Follow-up imaging
Patient 2
Baseline imaging
Follow-up imaging
Patient 3
Baseline imaging
Follow-up imaging