

# Should we thrombolys prior to endovascular treatment in acute stroke?

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## ABSTRACT

The superiority of endovascular treatment (EVT) in acute stroke due to large vessel occlusion has been proven in recent randomized trials. Yet, there are no randomized trials which have tested the additive effect of standard treatment with intravenous thrombolysis (IVT) as pretreatment to EVT over EVT treatment alone. So far, the EVT treatment groups of RCTs most often had pretreatment with IVT. The current guidelines on acute stroke treatment rely on meta-analyses and systematic analyses from RCTs and observational studies on pretreatment with IVT + EVT. Clinicians also apply their clinical experience and local “in-house” protocols.

We performed literature search on randomized controlled trials, systematic and meta-analyses and observational studies on recanalization therapies including intravenous thrombolysis and endovascular treatment or thrombectomy in acute stroke. Here we present a review and an opinion on the current choice of treatment modalities.

## 1. Introduction

The benefit of endovascular treatment for acute stroke patients is evident from 6 recent randomized trials of mechanical thrombectomy [1] and two latest trials on imaging-based extended treatment window, i.e. DAWN [2] and DEFUSE [3]. According to a meta-analysis [4], a mean of 96% of patients have received intravascular thrombolysis (IVT) with recombinant tissue plasminogen (rTPA i.e. alteplase) in the standard treatment group. The other way around in the endovascular treatment (EVT) group 82% had IVT as an adjunct treatment. There are no randomized trials (RCT) comparing the benefit of IVT + EVT over EVT alone.

Possible harms have been speculated as results of the combination therapy, like hemorrhagic complications, distal embolization due to fragmentation of the thrombus, delay in subsequent EVT, and high associated costs, besides preclusion of use of antiplatelets and heparin following tPA infusion [5]. On the other hand, combination therapy carries plausible benefits since tPA- induced fibrin degradation may lead to easier detachment of the clot with the stent-retriever, restore a

critical amount of blood flow, and potentially augments the collateral circulation in addition to recanalization of distal thrombi located in small vessels that are not accessible to endovascular devices [6,7]. Pretreatment with systemic thrombolysis in patients with large-vessel occlusion eligible for mechanical thrombectomy results in successful reperfusion in 1 of 10 cases [8].

Until we have data from RCTs (i.e., SWIFT-DIRECT, ClinicalTrials.gov Identifier: NCT03192332 and MR CLEAN no IV, DIRECT-SAFE) on the role of IVT prior to EVT we must rely on systematic analyses and meta-analyses besides observational studies. As clinicians we should also learn from our patients' experience.

## 2. Methods

TS performed a systematic literature search of the Ovid Medline database using the following search terms on 8.7.2018: exp Endovascular Procedures/ and exp Thrombectomy/ and exp Thrombolytic Therapy/ and exp Stroke/. Filter: Past 5 years, Publication Type: All Types. For details see Fig. 1. We also identified

*Abbreviations:* NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; MCA, middle cerebral artery; ACA, anterior cerebral artery; EVT, endovascular treatment; HUH, Helsinki University Hospital; M1, middle cerebral artery branch 1; IVT, intravenous thrombolysis; DSA, digital subtraction angiography

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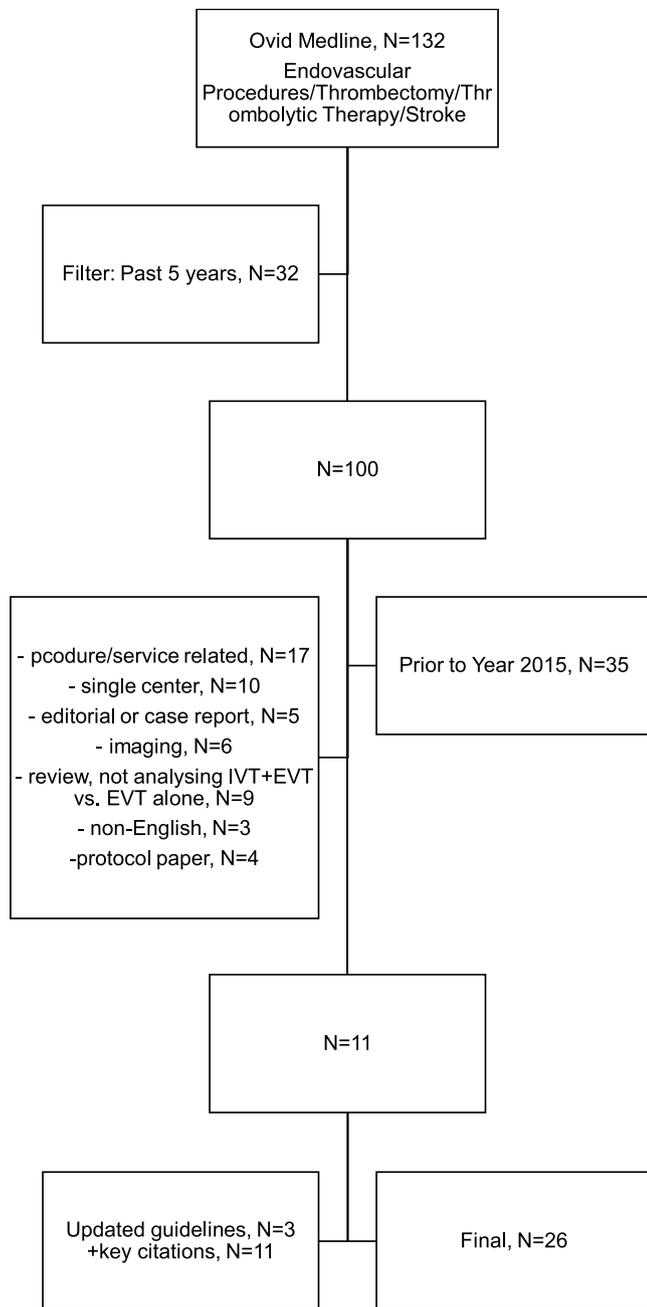


Fig. 1. Flowchart on the selection of literature.

updated guidelines on acute stroke treatment and key articles cited in them. Included literature yielded randomized controlled trials, systematic and meta-analyses and observational studies on recanalization therapies analyzing combined intravenous thrombolysis to endovascular treatment or thrombectomy in acute stroke.

### 3. Results

No randomized trials have tested the additive effect of IVT on EVT over EVT treatment alone. The EVT treatment groups of RCTs most often had pretreatment with IVT. Thus the current guidelines [9–11] rely on meta-analyses and systematic analyses from RCTs [4,12–19] and observational studies [20,21] on IVT + EVT. Clinicians also apply their clinical experience and local “in-house” protocols. Meta-analyses have shown the benefit of EVT over standard therapy. The main findings of studies included in this review [4,13–22] are summarized in Table 1. A meta-analysis including 8 RCTs, namely SYNTHESIS (2013), MR RESCUE (2013), IMS III (2013), MR CLEAN (2015), ESCAPE (2015), EXTEND-IA (2015), SWIFT-PRIME (2015) AND REVASCAT (2015) found an overall benefit of EVT over standard therapy of 1.71 (1.18–2.49;  $r^2 = 75.4\%$ ,  $p < 0.01$ ) in achieving functional independence [4]. In a subgroup analysis the odds ratio (OR) of 2.07 (1.46–2.92) for favorable outcome and reduced disability at 3 months was only seen in patients with IVT combined to EVT [4], a finding repeated by [16]. The HERMES meta-analysis [13] on five RCTs (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) confirmed the treatment benefit of thrombectomy in both alteplase pretreated and alteplase-ineligible patients. Yet, the small group of 188 non-alteplase treated patients were IVT-ineligible, and thus they represent a selected patient group.

To learn whether IVT-eligible patients benefit from combining IVT to EVT in a larger amount of patients, there is evidence from a systematic analysis on observational studies [20]. Comparison between somewhat larger groups of EVT- treated ( $n = 1268$ ) and EVT + IVT treated patients ( $n = 1334$ ) shows favorable outcome at 3 months with an OR of 0.80 (0.64–1.00;  $p = 0.05$ ) with EVT alone [20]. Similar benefit was evident in a Korean prospective multi-center registry [21]. A recent analysis on observational studies and RCTs resulted in a total number of 13 studies [22], and showed that patients with mechanical thrombectomy (MT) combined with IVT had higher rate of successful recanalization [(OR, 1.46 [95% CI, 1.09–1.96];  $P = 0.01$ )] and higher odds of good functional outcomes and lower mortality than MT patients without IVT [(mRS 0–2: OR, 1.27 [95% CI, 1.05–1.55],  $P = 0.02$ ); (mortality: OR, 0.71 [95% CI, 0.55–0.91],  $P = 0.006$ )], similar to Korean registry [21].

Safety of combined IVT + EVT is supported by the meta-analysis on the rate of symptomatic intracranial hemorrhage (sICH), which did not differ between EVT-group with 82% of patients with adjunct IVT-treatment and standard therapy group with a mean of 96% of patients

**Table 1**  
Summary of main findings in included studies [4,18–22].

Study	Study design	Intervention	Comparator	mRS	Recanalization	Safety measures
Badhiwala et al. [4]	Meta-analysis 8 trials, 2423 patients	EVT + IVT if eligible 1313 patients with EVT (82% had IVT as an adjunct treatment)	Standard medical care (IV tPA) 1110 with IV tPA	mRS at 3 months, mRS 0-2 EVT associated with treatment benefit across mRS (OR 1.56 [1.14–2.13]; P = 0.005) mRS 0-2 44.6% vs 31.8% (OR 1.71 [1.18–2.49]; P = 0.005)	Revascularization 75.8% vs 34.1% (OR 6.49 [4.79–8.79]; P < 0.001)	sICH within 90 days, mortality at 90 days sICH 5.7% vs 5.1% (OR 1.12 [0.77–1.63]; P = 0.56) Mortality 15.8% vs 17.8% (OR 0.87 [0.68–1.12]; P = 0.27 mRS 5-6 at 3 months 31.0% vs 19.0% (P = 0.041) in EVT vs IVT + EVT
Tsivgoulis et al. [12]	Meta-analysis 7 trials, 1764 patients	Direct EVT	IVT + EVT	No significant difference for IVT + EVT over EVT alone in terms of mRS at 90 days (OR 1.28 [0.91–1.89]; P = 0.155) mRS 0-2 41.7% vs 51.4% (P = 0.389) in EVT vs IVT + EVT		
Goyal et al. [13]	Meta-analysis 5 trials, 1287 patients	EVT + IVT if eligible 634 patients with EVT	Standard care 653 with standard care	mRS at 3 months, mRS 0-2 Reduced chance of disability at 90 days in EVT vs control (cOR 2.49 [1.76–3.53]; P < 0.0001) mRS 0-2 46.0% vs 26.5% (OR 2.35 [1.85–2.98]; P < 0.0001) mRS 0-2 at 3 months	Revascularization 71% in EVT group	Mortality at 90 days, sICH Mortality 15.3% vs 18.9% (OR 0.77 [0.54–1.10]; P = 0.16) sICH 4.4% vs 4.3% (OR 1.07 [0.62–1.80]; P = 0.81) Mortality at 90 days, sICH
Marmagkoulis et al. [14]	Meta-analysis 5 trials, 1287 patients	634 patients with EVT (83% had IVT as an adjunct treatment)	Standard care 653 with standard care	mRS 0-2 42.6% vs 26.1% (OR 2.43 [1.91–3.09]; P < 0.0001)		Mortality 15.1% vs 18.7% (RR 0.81 [0.58–1.12]; P = 0.19) sICH 4.2% vs 4.3% (RR 1.08 [0.64–1.82]; P = 0.78) sICH
Vidale et al. [15]	Meta-analysis 8 trials, 1845 patients	IVT + EVT 911 patients with IVT + EVT	Standard medical care 943 patients with standard care	mRS 0-2 at 3 months mRS 0-2 47.5% vs 31.6% (OR 2.087 [1.718–2.535]; P < 0.001)		sICH 3.4% vs 3.4% (OR 1.021 [0.641–1.629]; P = 0.739)
Yarbrough et al. [16]	Meta-analysis 8 trials, 2049 patients	EVT + IVT if eligible 1055 patients with EVT	Standard medical care 965 patients with standard care	mRS 0-2 at 3 months mRS 0-2 43.2% vs 30.9% (OR 1.75 [1.20–2.54])		Mortality at 90 days, sICH Mortality 15.36% vs 18.24% (OR 0.78 [0.57–1.08]) sICH no significant difference (OR 1.26 [0.80–1.98])
Bush et al. [17]	Meta-analysis 5 trials, 1287 patients	EVT + IVT if eligible 634 patients with EVT (83% had IVT as an adjunct treatment)	Standard care 653 with standard care	mRS at 3 months, mRS 0-2 2.22 times greater odds of better mRS at 3 months in EVT group ([1.66–2.98]; P < 0.0001) mRS 0-2 OR 2.47 [1.92–3.18]; P < 0.0001		Mortality, sICH No difference in Mortality (OR 0.78 [0.54–1.12]; P = 0.1056) No difference in sICH (OR 1.19 [0.69–2.05]; P = 0.5348)
Falk-Delgado et al. [18]	Meta-analysis 6 trials, 1943 patients	55% of patients EVT + IVT if eligible	Standard care 45% of patients	mRS 0-2 at 3 months mRS 0-2 46% vs 27% (OR 2.21 [1.78–2.74]; P < 0.00001)		Mortality at 90 days, sICH, mRS 5-6 at 90 days Mortality 15% vs 20% (OR 0.73 [0.56–0.96]; P = 0.02) sICH 5% vs 5% (OR 1.05 [0.65–1.68]; P = 0.85) mRS 5-6 23% vs 33% (OR 0.58 [0.46–0.73]; P < 0.00001)
Chen et al. [19]	Meta-analysis 8 trials, 2423 patients	EVT + IVT if eligible 1313 patients 75% had IVT as an adjunct treatment	Standard care 1110 patients	mRS 0-2 at 3 months mRS 0-2 43% vs 32% (OR 1.71 [1.18–2.49]; P = 0.005)		Mortality at 90 days, sICH Mortality 16.9% vs 18.4% (OR 0.87 [0.67–1.12]; P = 0.27) sICH 5.3% vs 4.8% (OR 1.12 [0.77–1.63]; P = 0.56)
Phan et al. [20]	Meta-analysis 12 trials, 2615 patients	Direct EVT 1275 patients	IVT + EVT 1340 patients	mRS 0-2 at 3 months mRS 0-2 44% vs 48% (OR 0.80 [0.64–1.002]; P = 0.052)		Mortality at 90 days, sICH Mortality 20.4% vs 19.4% (OR 1.19 [0.83–1.71]; P = 0.34) sICH 3.7% vs 3.8% (OR 0.98 [0.65–1.48]; P = 0.91)

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Table 1 (continued)

Study	Study design	Intervention	Comparator	mRS	Recanalization	Safety measures
Park et al. [21]	Observational study 639 patients	Direct EVT 181 patients	IVT + EVT 458 patients	mRS at 3 months, mRS 0-2 at 3 months IVT + EVT was associated with lower mRS scores (OR, 1.38 [0.98-1.96]) mRS 0-2 32% vs 39% (OR 1.27 [0.82-1.99]; P = 0.29)	Recanalization Recanalization 65% vs 73% (OR 1.96 [1.23-3.13]; P < 0.01)	Mortality at 90 days, sICH Mortality 24% vs 15% (OR 0.58 [0.35-0.97]; P = 0.04) sICH 11% vs 10% (OR 0.87 [0.44- 1.74]; P = 0.70)
Mistry et al. [22]	Meta-analysis 13 trials, 3553 patients	IVT + EVT 2221 patients	Direct EVT 1332 patients	mRS 0-2 at 3 months mRS 0-2 48.7% vs 44.3% (OR 1.27 [1.05-1.55]; P = 0.02)	Recanalization Recanalization 79.9% vs 76.2% (OR 1.46 [1.09-1.96]; P = 0.01)	Mortality at 90 days, sICH Mortality 14.8% vs 18.9% (OR 0.71 [0.55-0.91]; P = 0.006) sICH 4.6% vs 3.9% (OR 1.11 [0.69-1.77]; P = 0.67)

with IVT (5.3% vs. 4.8%; OR 1.12, 0.77–1.63) [4]. Similar sICH rates are evident in meta-analyses on RCTs as well [4,14,15,18]. According to systematic analysis of observational studies with EVT either alone or in combination with IVT, the rates of sICH were equal in 47 out of 1266 patients (3.7%) and 51/1332 (3.8%), respectively [20]. We have learned from the clinical experience that the development of a post-treatment sICH is most often multifactorial.

In a subgroup analysis of the HERMES collaboration [13] 108 patients in the direct EVT group had contraindications for IV t-PA and their outcome was grimmer with mRS 5 or 6 at 3 months in 30.5% of them compared with 19.6% in patients eligible for IVT + EVT combination treatment (n = 525). Contraindications to IVT need to be considered in each patient [23], as evidenced by a representative case with proximal occlusion of ICA with low probability of recanalization besides high risk of sICH due to known microbleeds and a previous ICH (Fig. 2A–D).

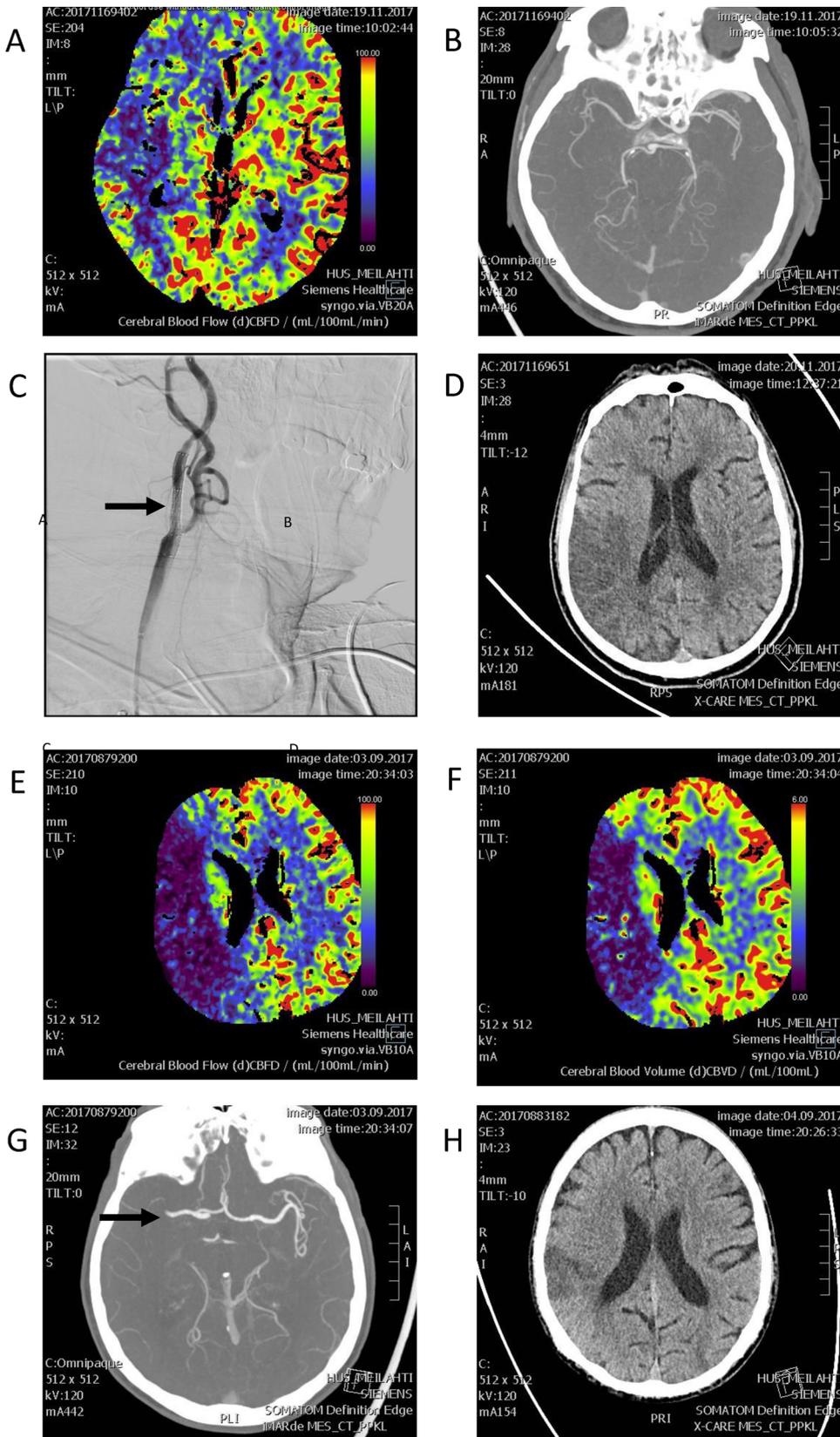
The IVT should not be delayed even though the patient is a candidate for EVT [7]. Decision making is not always easy although we can apply sophisticated perfusion software [23] as demonstrated also by a patient shown in Fig. 2E–H. The cerebral blood flow (Fig. 1E) and blood volume (1F) maps had large deficit which were almost equal thus suggesting only a small mismatch and a large core. The patient had moderate hemispheric collaterals and showed early ischemic changes on native CT scan (cortical sulcal flattening, not shown). No complications developed due to IVT and recanalization was achieved by it. Furthermore, final infarct size that was smaller than cerebral blood volume predicted (Fig. 1H). Multimodal imaging is not to be applied for a decision not to perform IVT or EVT if patient presents inside treatment window [24]. The decision making is always individualized [11].

If IVT-bridging is not administered, long transportation times for EVT may turn into less benefit from treatment. In case of unsuccessful EVT, no treatment is delivered. There is a possibility of delaying diagnosis of an ICH, if direct transport to EVT-hospital prolongs transportation times. In basilar artery occlusion we don't know which patients benefit the most from EVT while waiting for the results of BASICS registry (ClinicalTrials.gov Identifier: NCT01717755). There are situations where IVT is mostly ineffective, including ICA occlusion (ICAO) [8]. Although the probability of rapid recanalization is low (4% at 2 h), there is a potentially relevant later incidence of intracranial reperfusion with IVT for ICA occlusion (28% at 24 h according to IMS 3 data) [25]. ICAO may also be treated with stenting as an acute treatment option adjunctive to EVT (Fig. 1C). Also contraindications such as microbleeds [26], previous ICH and late presentation for IVT treatment window, leave the stage for EVT without IVT [23].

#### 4. Conclusion

Until we have data from RCTs (like SWIFT-DIRECT and MR CLEAN no IV, DIRECT-SAFE), we use combined data from randomized trials and observational studies on patients eligible for IVT + EVT. Based on them the IVT + EVT group most probably gains better functional outcomes, probably also lower mortality, and a higher rate of successful recanalization. In the presence of a proximal arterial occlusion on angiographic imaging use of stent retriever devices for mechanical thrombectomy, and in most of the cases intravenous tPA combined with endovascular intervention, are important factors associated with improved functional outcomes related to endovascular thrombectomy.

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**Fig. 2.** Representative patient cases.

A) An 80-year old male patient with previous history of hypertension and prostate cancer. Two years earlier he had an ICH due to amyloid angiopathy with known microbleeds. At 8.40 o'clock, he developed left hemiparesis with NIHSS score of 15. On the head CT perfusion scan, large cerebral blood flow deficit was seen in the areas of right MCA and ACA (A) and a large parietal cerebral blood volume deficit as well (not shown). CT-angiogram showed patent MCA (B) and right ICA occlusion (not shown). No IVT treatment was considered reasonable due to proximal occlusion of ICA with low probability of recanalization besides high risk of sICH due to known microbleeds and a previous ICH. Patient was treated with thrombectomy and stenting of the right ICA (arrow in C). After endovascular treatment, amelioration in left motor hemiparesis was achieved, but the patient developed delirium predisposed by age and microangiopathy. The medical treatment after EVT and stenting was low-dose of low molecular weight heparin as deep vein thrombosis prophylaxis and clopidogrel as antiplatelet monotherapy due to the large size of the final infarct besides microangiopathy.

E) 73-year old male, with hypertension. On a cruise at 18:20 o'clock, he developed left hemiparesis. He was transported with a helicopter to HUCH. He was investigated at 20:15 and had NIHSS score of 11. On the head CT scan dense media sign was seen (not shown), besides large deficit in both cerebral blood flow (E) and volume (F) maps. The CT-angiogram verified MI-occlusion (arrow in G). IVT was started at 20:25 (2 h 5 min). On a subsequent DSA, the right MCA was recanalized by IVT, verified at 21:30. After treatment patient still had left hemiparesis with ameliorated neglect. The final infarct size was smaller than the cerebral blood volume of the perfusion scan (H).

## Authors contribution

Authors' role in the manuscript. TS, JR: Substantial contribution to conception and design, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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