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ORIGINAL COMMUNICATION

Intravenous thrombolysis or endovascular therapy for acute ischemic stroke associated with cervical internal carotid artery occlusion: the ICARO-3 study

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Abstract The aim of the ICARO-3 study was to evaluate whether intra-arterial treatment, compared to intravenous thrombolysis, increases the rate of favourable functional outcome at 3 months in acute ischemic stroke and extra-

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cranial ICA occlusion. ICARO-3 was a non-randomized therapeutic trial that performed a non-blind assessment of outcomes using retrospective data collected prospectively from 37 centres in 7 countries. Patients treated with endovascular treatment within 6 h from stroke onset (cases) were matched with patients treated with intravenous thrombolysis within 4.5 h from symptom onset (controls). Patients receiving either intravenous or endovascular therapy were included among the cases. The efficacy outcome was disability at 90 days assessed by the modified Rankin Scale (mRS), dichotomized as favourable (score of 0–2) or unfavourable (score of 3–6). Safety outcomes were death and any intracranial bleeding. Included in the analysis were 324 cases and 324 controls: 105 cases (32.4 %) had a favourable outcome as compared with 89 controls (27.4 %) [adjusted odds ratio (OR) 1.25, 95 % confidence interval (CI) 0.88–1.79, $p = 0.1$]. In the adjusted analysis, treatment with intra-arterial procedures was significantly associated with a reduction of mortality (OR 0.61, 95 % CI 0.40–0.93, $p = 0.022$). The rates of patients with severe disability or death (mRS 5–6) were similar in cases and controls (30.5 versus 32.4 %, $p = 0.67$). For the ordinal analysis, adjusted for age, sex, NIHSS, presence of diabetes mellitus and atrial fibrillation, the common odds ratio was 1.15 (95 % IC 0.86–1.54), $p = 0.33$. There were more cases of intracranial bleeding (37.0 versus 17.3 %, $p = 0.0001$) in the intra-arterial procedure group than in the intravenous group. After the exclusion of the 135 cases treated with the combination of I.V. thrombolysis and I.A. procedures, 67/189 of those treated with I.A. procedures (35.3 %) had a favourable outcome, compared to 89/324 of those treated with I.V. thrombolysis (27.4 %) (adjusted OR 1.75, 95 % CI 1.00–3.03, $p = 0.05$). Endovascular treatment of patients with acute ICA occlusion did not result in a better functional outcome than treatment with intravenous thrombolysis, but was associated with a higher rate of intracranial bleeding. Overall mortality was significantly reduced in patients treated with endovascular treatment but the rates of patients with severe disability or death were similar. When excluding all patients treated with the combination of I.V. thrombolysis and I.A. procedures, a potential benefit of I.A. treatment alone compared to I.V. thrombolysis was observed.

Keywords Acute stroke · Thrombolysis · Endovascular procedures

Background

In patients with acute ischemic stroke, intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is recommended as soon as intracranial haemorrhage is ruled out by computed tomography (CT) [1–3]. Intra-arterial (IA) therapy results in higher recanalization rates when compared to IV thrombolysis alone, but randomized trials have failed to demonstrate the superiority of endovascular approaches in terms of clinical outcome [4–6].

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Systemic thrombolysis in patients with occlusion of the internal carotid artery (ICA) is associated with low complete recanalization rates and poor clinical outcome [7–9]. In these patients, the ICARO (Intravenous Thrombolysis or Endovascular Therapy for Acute Ischemic Stroke Associated With Cervical Internal Carotid Artery Occlusion) study compared efficacy of IV rt-PA within 4.5 h from symptom onset to controls not treated with thrombolysis. The administration of thrombolysis resulted in a significant increase in the proportion of patients not dependent for activities of daily living but increases in death and any intracranial bleeding were the trade-offs for this clinical benefit [10]. A meta-analysis of non-randomized trials suggests that endovascular treatment of stroke attributable to ICA occlusion might lead to improved functional outcomes, compared to systemic thrombolysis alone [11]. However, a few data exist regarding the treatment of stroke in patients with extracranial ICA occlusion.

The ICARO-3 study in patients with acute ischemic stroke and extracranial ICA occlusion was aimed at determining whether endovascular treatment performed within 6 h from stroke onset increases the proportion of independent survivors at three months in comparison to systemic intravenous thrombolysis with rt-PA, administered according to European labelling (within 4.5 h from stroke onset).

Patients and methods

Patient population and study design

ICARO-3 was a non-randomized therapeutic trial that performed a non-blind assessment of outcomes using retrospective data collected prospectively from 37 centres in 7 countries. Cases were consecutive patients with acute ischemic stroke and extracranial ICA occlusion on admission treated with endovascular treatment within 6 h from symptom onset. Patients with tandem occlusion (extracranial ICA and middle cerebral artery) were not excluded. Controls were patients with acute ischemic stroke and extracranial ICA occlusion treated with intravenous rt-PA within 4.5 h from symptom onset. Controls were selected from a series of 418 consecutive patients treated with IV thrombolysis (253 patients were included in the ICARO-1 study) [10]. Cases and controls were matched for age, gender, and severity of stroke, using the NIHSS scale for the latter. ICA occlusions were diagnosed either by carotid ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA) or angiography [12, 13]. For each patient, physicians were free to decide about treatment with IV or IA procedures according to the clinical picture and/or neuroradiological reports.

The matching procedure was performed in absence of any information about the patient's final outcome. Inclusion and exclusion criteria were those of the SITS-MOST study [14], except for the 80-year age limit. Patients of both genders were eligible for inclusion in the study if they were older than 18 years of age and had a clinical diagnosis of acute ischemic stroke associated with ICA occlusion. Acute stroke was defined as sudden onset of an acute focal neurological deficit, such as impairment of language, motor function, cognition, gaze, vision, or neglect (or a combination of these). On admission, a cerebral CT scan was required to exclude patients with intracranial bleeding. In some cases, MRI was performed instead of CT.

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Cases received intra-arterial thrombolysis which was, if necessary, associated to or substituted by mechanical clot disruption and/or retrieval. Patients who received both intravenous and endovascular therapy were included among the cases. For pharmacologic IA thrombolysis, a microcatheter was to be positioned close to (or within or beyond) the thrombus with the use of a microguide; the t-PA dose infused did not exceed 0.9 mg per kilogram of body weight (maximum, 90 mg for patients with a body weight of $\geq$100 kg): if urokinase was used, the full dose infused did not exceed 1,200,000 Units. If complete recanalization was achieved before the maximum dose was reached, the infusion of thrombolytic was stopped. The option of mechanical embolectomy was left to each interventionist's discretion. Mechanical embolectomy could involve the use of a microguidewire to facilitate disintegration of the thrombus, systems to capture and extract the thrombus, or more complex systems to crush and aspirate it.

Controls received 0.9 mg of rt-PA (Actilyse; Boehringer Ingelheim or Activase; Genetech) per kilogram, administered intravenously (with an upper limit of 90 mg). Of the total dose, 10 % was administered as a bolus and the remainder was administered by continuous intravenous infusion over a period of 60 min. Neurological deficit was assessed using the National Institute of Health Stroke Scale (NIHSS). Follow-up neuroimaging was performed between 24 and 36 h after admission. Further brain CT scans were performed at discretion of the investigators. Patients gave informed consent to treatments and to retrieval of data and follow-up procedures, according to the regulations of participating countries. The study was approved by the local Institutional Review Board (IRB), if required. Patients gave informed consent to be treated with endovascular therapy.

Outcome measures

The primary efficacy study outcome was disability at day 90 (3-month visit), as assessed by means of the modified Rankin scale (mRS), dichotomized as favourable outcome (score of 0–2) or unfavourable outcome (score of 3–6). The score was determined at clinical examination or by phone interview. Safety outcomes were overall mortality at day 90, any intracranial bleeding [2], fatal intracranial bleeding, and other serious adverse events. An adverse event was serious when considered life threatening, required hospitalization or its prolongation or resulted in a permanent damage.

Statistical analysis

Comparisons of the unmatched features in the endovascular and intravenous groups were performed using the Mann–Whitney *U* test. Data were given as mean and standard deviation ($\pm$SD) or median with interquartile range when appropriate. For the outcome measures, differences between groups were calculated with the Mann–Whitney *U* test. Ninety-five percent CI were calculated for odds ratio (OR). An adjusted analysis (logistic regression) of the study outcomes was performed. This analysis was performed by including study group assignment, diabetes and presence of atrial fibrillation in the model. The variables included were selected because those were different at baseline ($p < 0.1$) between cases and controls.

Furthermore, an ordinal logistic regression analysis was performed in which the mRS (dependent variable) had 6 levels: levels 5 and 6 were combined into a single level and levels 0, 1, 2, 3, 4 were retained as distinct [15]. In this model the treatment odds ratios between one level and the next were assumed to be constant, so a single parameter (common OR) summarizes the shift in outcome distribution between cases and controls.

The calculation of the sample size was based on an anticipated increase in the rate of patients with favourable outcome at 3 months (mRS score 0–2) from 28 % in the intravenous-treated group [9, 10] to 38 % in the endovascular-treated group [11], for an alpha 0.05 and a power of 80 %. On the basis of these data, we anticipated that at least 324 patients per group were required.

Results

Data were collected from January 2010 and August 2013. We analysed 648 patients; 324 cases (43 with tandem occlusion) and 324 controls were included in the final analysis. Times from stroke onset to treatment were available for 423 patients (239 of the patients treated with I.V. thrombolysis and 184 of the patients treated with I.A. procedures): median treatment time for I.V. thrombolysis was 154 min (IQR 130–180); median treatment time for I.A. procedure alone was 240 min (IQR 180–297.5); and median treatment time for the combination of I.V. and I.A. procedures was 155 min (IQR 109.5–258) ($p = 0.001$ and $p = 0.05$, using the I.V. group as reference). Baseline demographic and clinical characteristics of the two groups were similar (Table 1): 105 cases (32.4 %) had a favourable outcome (mRS score 0 to 2 at 3 months) as compared with 89 controls (27.4 %) [unadjusted odds ratio (OR), 1.25; 95 % confidence interval (CI), 0.90–1.77; $p = 0.1$]. In the adjusted analysis, treatment with I.A. procedures was not associated with a favourable outcome (adjusted OR 1.25, 95 % CI 0.88–1.79, $p = 0.1$). The results of the analysis related to functional outcomes are summarized in Table 2. A further analysis of mRS score 0–1 at 3 months was also performed; 67 cases (20.7 %) had mRS score 0–1,

Table 1 Demographic and baseline patient characteristics

	I.A. procedures ($n = 324$)	I.V. rt-PA ($n = 324$)	P
Age (year, mean)	62.9 ± 13.4	63.5 ± 12.9	0.5
Median (IQR)	65 (54–73)	66 (54–74)	
Male sex	205 (63.3 %)	205 (63.3 %)	1.0
NIHSS score			
Mean	15.8 ± 6.1	15.6 ± 5.4	0.6
Median (IQR)	16 (11–20)	16 (12–20)	
Systolic pressure (mmHg)			
Mean	148.3 ± 26.3	149.9 ± 23.1	0.4
Median (IQR)	145 (130–165)	150 (135.5–165)	
Diastolic pressure (mmHg)			
Mean	83.0 ± 14.6	82.7 ± 13.1	0.8
Median (IQR)	81 (74–90)	80 (75–90)	
Glycemia (mg/dL)			
Mean	140.3 ± 70.4	137.1 ± 65.0	0.6
Median (IQR)	122.5 (103–147)	120 (106–146)	
Atherosclerosis[b]	168 (51.8 %)	178 (54.9 %)	0.5
Dissection	36 (11.1 %)	45 (13.8 %)	0.3
Atrial fibrillation or flutter	62 (19.1 %)	46 (14.2 %)	0.1
Diabetes mellitus	78 (24.0 %)	61 (18.8 %)	0.1
Hypertension	205 (63.2 %)	193 (59.7 %)	0.3
Hyperlipidemia	98 (30.2 %)	101 (31.1 %)	0.8
Previous use of antiplatelets	68 (22.1 %)	84 (27.3 %)	0.6
Previous use of statins	33 (10.7 %)	48 (15.6 %)	0.2
History of stroke/TIA	29 (8.9 %)	35 (10.8 %)	0.9
Current smoker	110 (33.9 %)	112 (34.5 %)	0.9
Diagnosis of ICA occlusion			
Ultrasound	–	163 (50.3 %)	
CTA	–	113 (34.9 %)	
MRA	–	47 (14.5 %)	
Angiography	324 (100 %)	1 (0.3 %)	
Tandem occlusion	43 (13.2 %)	22 (13.6 %)[a]	1.0
I.A. procedures			
	41 I.A. thrombolysis		
	71 mechanical (13 stenting)		
	77 I.A. thrombolysis and mechanical (17 stenting)		
	135 Combination I.V. and I.A. procedures		
	80 I.V. + I.A. thrombolysis		
	38 I.V. + mechanical (8 stenting)		
	17 I.V. + I.A. thrombolysis + mechanical (13 stenting)		

I.V. intravenous thrombolysis, *I.A.* intra-arterial

[a] Out from 161 patients that performed angio CTA or MRA

[b] Atherosclerosis was considered present if there was a visible plaque on ultrasound or neuroimaging

as compared with 59 controls (18.2 %) (OR 1.17, 95 % CI 0.79–1.73, $p = 0.5$). In the adjusted analysis, treatment with I.A. procedures remained not associated with a mRS score 0–1 at 3 months (OR 1.12, 95 % CI 0.77–1.63, $p = 1.0$). The rates of patients with severe disability or death (mRS 5–6) were similar in cases and controls (30.5 versus 32.4 %, $p = 0.67$).

The overall distribution of scores by the modified Rankin scale is shown in the Fig. 1. For the ordinal analysis, adjusted for age, sex, NIHSS, presence of diabetes mellitus

Table 2 Efficacy and safety endpoints

	I.A. procedures ($n = 324$) (%)	I.V. rt-PA ($n = 324$)	OR (95 % CI)	P
Efficacy endpoints				
Favourable outcome (mRS 0–2)	105 (32.4)	89 (27.4)		
Unadjusted analysis			1.27 (0.90–1.77)	0.1
Adjusted analysis			1.25 (0.88–1.79)	0.1
Favourable outcome (mRS 0–1)	67 (20.7)	59 (18.2)		
Unadjusted analysis			1.17 (0.79–1.73)	0.5
Adjusted analysis			1.10 (0.77–1.63)	1.0
Safety endpoints				
Any ICH	120 (37.0)	56 (17.3)	2.82 (1.95–4.06)	0.0001
HI*	70 (21.7)	42 (13.0)		0.005
PH*	50 (15.3)	14 (4.3)		0.0001
Fatal ICH	19 (5.9)	7 (2.2)	3.31 (1.30–8.40)	0.01
Death	57 (17.6)	75 (23.1)		
Unadjusted analysis			0.71 (0.48–1.04)	0.07
Adjusted analysis			0.61 (0.40–0.93)	0.022

CI indicates confidence interval, *ICH* intracerebral haemorrhage, *HI* hemorrhagic infarct, *mRS* Modified Rankin scale, *OR* odds ratio, *PH* parenchymal hematoma [24], *rt-PA* recombinant tissue-type plasminogen activator

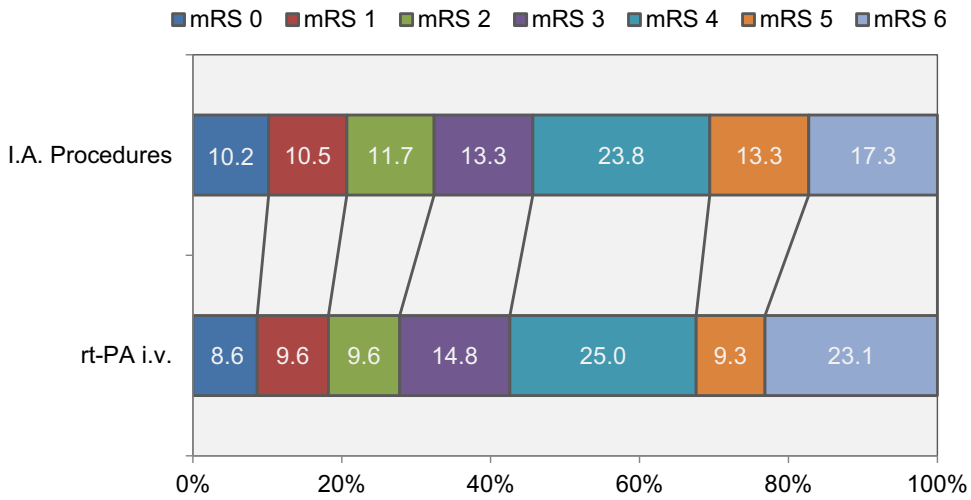

Fig. 1 The Overall Distribution of Scores According to the modified Rankin Scale

and atrial fibrillation, the common odds ratio was 1.15 (95 % IC 0.86–1.54), $p = 0.33$.

In Table 3, the intra-arterial procedures and their relative outcomes are described. Patients treated with mechanical procedures associated with I.V. or I.A. thrombolysis had a better outcome compared to patients treated with the other endovascular approaches.

Regarding reperfusion, 265 patients of the patients treated with endovascular procedures had TICI score [16]: 182 patients (68.7 %) had TICI score 2 (a, b) or 3. Among these 182 patients, 47.2 % had mRS 0–2 at 90 days compared to 6 % of the 83 patients with TICI score 0–1.

Safety

A total of 132 out of 648 patients died (20.4 %), 57 cases (17.6 %) and 75 controls (23.1 %): (OR 0.71, 95 % CI 0.48–1.04, $p = 0.07$). In the adjusted analysis, treatment with I.A. procedures was significantly associated with a reduction of mortality (OR 0.61, 95 % CI 0.40–0.93, $p = 0.022$). In the I.V. group compared to I.A. procedures group, there were significantly more cases of fatal malignant oedema [29 patients (9.0 %) and 13 patients (4.1 %), respectively; $p = 0.01$] and more cases of death due to stroke progression [12 patients (3.7 %) and 4 patients (1.2 %), respectively; $p = 0.04$].

Table 3 The intra-arterial procedures and their relative outcomes

	mRS 0–2 (%)	Mortality (%)	Fatal ICH
IV t-PA	27.4	23.1	2.2
IA thrombolysis alone (41)	17.0	39.0	4.9
Mechanical alone (71)	25.3	23.9	8.4
IA thrombolysis and mechanical (77)	42.8*	14.2	2.6
IV t-PA + IA procedures (135)	28.1	16.3	6.6
IV t-PA + IA thrombolysis (80)	22.5	15.0	5.0
IV t-PA + Mechanical (38)	42.1**	13.1	7.9
IV t-PA + IA thrombolysis − mechanical (17)	23.5	29.4	11.7

* $p = 0.01$

** $p = 0.09$

There were more cases of intracranial bleeding (37.0 versus 17.3 %, OR 2.82, 95 % CI 1.95–4.06, $p = 0.0001$) and fatal intracranial bleeding (5.8 versus 2.2 %, OR 3.31, 95 % CI 1.30–8.40, $p = 0.01$) among I.A. procedure group than in the I.V. group. Nineteen patients (5.9 %) had other serious adverse events related to treatment with I.A. procedures (4 cases of femoral hematoma, 3 cases of agitation requiring intubation, 3 distal embolisations, 2 external carotid dissections, 1 internal carotid dissection, 2 subarachnoid haemorrhages, 2 cases of epileptic seizures, 1 case of bradycardia requiring atropine, and 1 case of severe hypotension) and 6 (1.8 %) related to I.V. rt-PA treatment (2 cases of severe hypertension, 1 case of severe hypotension, 1 case of severe vomiting, 1 case of epileptic seizure and 1 tongue edema case). No patients had severe extracranial bleedings.

Additional analyses

According to the study design, the I.A. group included patients treated with a combination of I.V. thrombolysis and I.A. procedures. In this subgroup, the initial treatment intention (planned versus rescued) could not be identified. Therefore, to reduce selection bias we performed an additional analysis that excluded 135 cases of patients treated with the I.V. and I.A. combination. Afterwards, we performed a sensitivity analysis that included this combination subgroup in the I.V. treatment arm.

Baseline demographic and clinical characteristics of the two groups, after excluding from the cases patients treated with the combination of I.V. thrombolysis and I.A. procedures, were balanced except for the presence of AF which was more prevalent in patients treated with the I.A. procedures: 43/189 (22.6 %) versus 46/324 (14.2 %), $p = 0.016$. Regarding functional outcome, 67/189 patients treated with I.A. procedures (35.3 %) had an apparent favourable outcome (mRS score 0 to 2 at 3 months) compared to 89/324 patients treated with I.V. thrombolysis (27.4 %) (unadjusted OR 1.43, 95 % CI 0.98–2.11, $p = 0.074$). In the adjusted analysis, treatment with I.A. procedures was associated with a favourable outcome (adjusted OR 1.75, 95 % CI 1.00–3.03, $p = 0.05$). Regarding mortality, 35 patients treated with I.A. procedures died (18.4 %) compared to 75 patients treated with I.V. thrombolysis (23.1 %): (unadjusted analysis OR 0.75, 95 % CI 0.47–1.17, $p = 0.22$; adjusted analysis OR 0.69, 95 % CI 0.39 –1.22, $p = 0.19$). There were more cases of intracranial bleeding (37.9 versus 17.3 %, OR 2.92, 95 % CI 1.93–4.40, $p = 0.0001$) and fatal intracranial bleeding (5.3 versus 2.2 %, OR 2.51, 95 % CI 0.94–6.72, $p = 0.11$) in the I.A. procedure group, compared to the I.V. group.

Baseline demographic and clinical characteristics of the two groups after adding to control group patients treated with the combination of I.V. thrombolysis and I.A. procedures, were balanced except for the presence of AF which was more prevalent in patients treated with I.A. procedures: 43/189 (22.6 %) versus 65/458 (14.2 %), $p = 0.015$. Regarding functional outcome, 67/189 patients treated with I.A. procedures (35.3 %) had a favourable outcome (mRS score 0 to 2 at 3 months) compared to 126/458 patients treated with I.V. thrombolysis or with the combination of I.V. thrombolysis and I.A. procedures (27.6 %) (unadjusted OR 1.43, 95 % CI 0.99–2.06, $p = 0.06$). In the adjusted analysis, treatment with I.A. procedures alone was associated with a favourable outcome but it was not statistically significant (adjusted OR 1.67, 95 % CI 0.98–2.78, $p = 0.06$). Regarding mortality, 35 patients treated with I.A. procedures died (18.4 %) compared to 97 patients treated with I.V. thrombolysis or with the combination of I.V. thrombolysis and I.A. (21.3 %): (unadjusted analysis OR 0.84, 95 % CI 0.54–1.29, $p = 0.39$, adjusted analysis OR 0.67, 95 % CI, 0.38–1.16, $p = 0.14$). There were more cases of intracranial bleeding (37.9 versus 22.8 %, OR 3.22, 95 % CI 2.04–5.00, $p = 0.0001$) and fatal intracranial bleeding (5.3 versus 3.5 %, OR 1.10, 95 % CI 0.68–3.44, $p = 0.84$) among I.A. procedures alone group.

Discussion

This multicentre study, which was powered to detect an advantage of 10 percentage points with endovascular treatment for the primary outcome, failed to show the superiority of endovascular therapy, compared to intravenous rt-PA in patients with extracranial ICA occlusion. Also ordinal shift analysis failed to demonstrate differences in final outcome between cases and controls. The disability free survival rate was 5 percentage points lower after endovascular treatment than after intravenous rt-PA. A larger

sample size might have allowed better discrimination between effects in these patients. In fact, to reach an efficacy of endovascular procedures, 1,300 patients per group to detect a 5 % absolute risk reduction need to be included.

In the ICARO-3 study, several types of devices and several types of endovascular approaches were used: the combination of intravenous and intra-arterial thrombolysis or intra-arterial thrombolysis alone. Alternatively, some patients with ICA occlusion received rescue interventional therapies, such as intra-arterial thrombolysis and mechanical thrombectomy, whenever intravenous thrombolysis failed to achieve recanalization. To avoid treatment delay, some centres also used bridging at the start of intravenous thrombolysis, while endovascular treatment was being planned. For this, we chose to include patients treated with bridging therapy as cases. These non-standardized endovascular methods could have determined heterogeneity in the results.

Device technology is advancing rapidly and recent randomized studies have clearly shown that stent retrievers are more efficacious than the devices currently used in clinical practice [17, 18]. Outcomes with early endovascular techniques are limited by long procedure times. The newest stent-based thrombectomy devices allow for rapid complete recanalization rates in occlusion of the proximal middle cerebral artery with better outcomes, when compared to I.V. rt-PA [19]. The ICARO-3 study did not investigate for the effect of specific device, in fact, as in the SYNTHESIS and IMS-3 trials [4, 6], the ICARO-3 study results reflect the devices available when it was conducted.

Our study had several limitations. First, since some of the patients treated with IV rt-PA had ICA occlusion diagnosed on ultrasonography, we do not know how many patients had tandem intracranial occlusion to compare these with those with tandem occlusion in the endovascular group [20, 21]. For this reason, we chose also to include patients with tandem occlusion. Second, we used two different time windows, 6 h for endovascular treatments and 4.5 h for I.V. treatment. This difference could have influenced the final results due to the fact that patients in the latter were treated earlier. Our analysis evidenced that the risk of intracranial bleedings was significantly higher in patients who had been treated with an endovascular approach. This difference in the results could have been due to a delay in treatment. But in clinical practice, the time required to perform endovascular procedures is generally longer. Third, the design of the study does not allow to know why IA treatment was chosen instead of IV treatment in the group of patients treated by IA treatment alone. Some patients may have been treated by IA thrombolysis because the delay between stroke onset and treatment was too long for IV treatment. Moreover, some patients could have received IA treatment because the intravenous treatment had failed. The inclusion of these patients in the group treated by IA treatment may have increased the proportion of patients with a good prognosis in the group of patients treated only with IV rt-PA. When excluding the patients treated with bridging therapy, or adding them to the I.V. group, a slightly significant trend in favour of I.A. treatment was observed. This suggests that an adequate sample size might have evidenced a statistically significant difference between the two groups. No data are available concerning the initial volumes of infarcts as not all patients have had MRI. Also, we do not have the initial ASPECTS scores. We cannot exclude an imbalance between the two groups of patients concerning initial stroke lesion volume as this has prognostic implications [22]. Probably, some centres used core or perfusion imaging to select patients for therapy. This could have been an additional confounder, since patients with favourable perfusion/core patterns tend to have better outcomes than those without favourable perfusion/core patterns. Furthermore, cases and controls were matched for age, gender and stroke severity and we cannot exclude the possibility of overmatching, which would have decreased the possibility of finding a difference between the two interventions. Other limitations include a lack of both central adjudication of the outcome events as well as vascular imaging for an accurate diagnosis of ICA occlusion and its reperfusion.

Concerning the diagnosis of ICA occlusion, three different imaging methods were used in controls. The accuracy of these methods in the diagnosis of ICA occlusion, compared to the gold standard (digital angiography) is considered high. Indeed, MRA has a sensitivity of 98 % and a specificity of 100 % compared to digital angiography, whereas CT angiography has a sensitivity of 97 % and a specificity of 99 %. Ultrasound examination has a sensitivity of 96 % and a specificity of 100 % [12, 13, 23]. Given the above, we believe that the use of these methods for the diagnosis of ICA occlusion did not significantly influence the results of the study.

The strengths of our study included its adequate sample size of patients, cases and controls were matched for risk factors, and this matching procedure was performed in blind manner for the clinical outcome.

In conclusion, this study failed to detect an advantage of 10 percentage points with endovascular treatment for the primary outcome compared to intravenous rt-PA in patients with extracranial ICA occlusion. A higher rate of intracranial bleeding after endovascular treatment did not result in an increased overall mortality rate that was significantly reduced, compared to patients treated with I.V. rt-PA but the rates of patients with severe disability or death were similar. After excluding patients treated with the combination therapy, a potential benefit of I.A. treatment alone was observed in comparison to I.V. thrombolysis. In view

of the non-randomized nature of this study, these results should be interpreted with caution.

Conflicts of interest The study was conducted under the nonfinancial auspices of the Italian Stroke Association. M.P. received honoraria as a member of the speaker bureau of Sanofi-Aventis. G.A. received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. D.L. has had consultancy roles for and has contributed to advisory boards, steering committees, and adjudication committees for Sanofi-Aventis, Servier, Boehringer Ingelheim, AstraZeneca, Novo-Nordisk, Allergan, Bayer, Ebewe, CoLucid Pharma, Brainsgate, Photothera, Lundbeck, and GSK, fees for which were paid toward research at ADRINORD (Association pour le Développement de la Recherche et de l'Innovation dans le Nord-Pas de Calais) or the research account of the hospital (délégation a' la recherche du CHU de Lille). He was reimbursed for travel or accommodation expenses needed for the participation on these boards and committees. He was associate editor of the Journal of Neurology, Neurosurgery and Psychiatry from 2004 to 2010. GT has been supported by European Regional Development Fund—Project FNUSA-ICRC (N. CZ.1.05/1.1.00/02.0123). D.T. was paid for expert testimony by Boehringer Ingelheim, Pfizer, and Sanofi-Aventis. The other authors have nothing to disclose.

Ethical standards The study has been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

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