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Time is brain: timing of revascularization of brain arteries in stroke

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Ischaemic stroke is the second leading cause of mortality and disability in the western world. Revascularization interventions are the cornerstone of the acute treatment of this pathology and must be administered as soon as possible after the patient's arrival. They consist of intravenous thrombolysis (IVT) with alteplase, recommended by the guidelines within 4.5 h of the onset of symptoms, and endovascular treatment, recommended within 6 h of the onset of symptoms. The individualized patient selection based on the extent of the mismatch between the penumbra and the ischaemic core allowed to overcome the limits imposed by the rigid time windows, defining a benefit of mechanical revascularization therapies up to 24 h from the theoretical onset of symptoms (last time the patient was known to be well) and up to 9 h for IVT since the theoretical onset of symptoms (last time the patient was known to be well). Advanced neuroimaging methods with perfusion studies are a fundamental tool in patient selection. Their spread in the territory, together with a greater availability of neurovascular treatment units are desirable to ensure a fair delivery of treatment to all patients with ischaemic stroke.

Introduction

The treatment of acute ischaemic stroke (AIS) is based on pharmacological or mechanical revascularization therapies that can be delivered within specific time windows. Intravenous thrombolysis (IVT), through the administration of alteplase, is recommended by the guidelines within 4.5 h of the onset of symptoms, endovascular treatment (EVT) is recommended within 6 h in the presence of large vessel occlusion (LVO) at neuroimaging.[1–3]

Time is a key factor in the effectiveness of reperfusion therapy. In fact, the current guidelines indicate as optimal goal a door to needle time of less than 60 min in more than 50% of patients with AIS. As a result of ischaemia, on average 1.9 million neurons are lost every minute and considering the neuronal loss induced by normal ageing, for every hour after an arterial occlusion the brain ages 3.6 years. Several studies showed how infarct volume increases in patients who do not achieve adequate reperfusion after ischaemia, leading to increased mortality and disability. The analysis of data from the 'Get With The Guidelines-Stroke Program' registry, evaluating 58 353 patients with acute ischaemic stroke who received IVT in the USA within 4.5 h from the onset of symptoms, found that the benefit of therapy decreased over the time, and every 15 min of reduction in the administration time of alteplase were associated with an increase in the probability of return to walk independently at discharge time and discharge at home rather than in rehabilitation institution, and a reduced incidence of symptomatic intracranial Haemorrhage (sICH) and in-hospital mortality.[4]

As regards EVT, a meta-analysis of the study group Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trials (Hermes) showed that out of 1000 patients undergoing treatment, for every 15 min of reduction of the door to reperfusion time 39 more patients would have a less disabled outcome at 90 days, including 25 more who would achieve functional independence (defined as a modified Rankin Scale score, mRS, equal to 0–2). Furthermore, the meta-analysis indicated how this benefit was closely

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linked to time and how the effectiveness of the treatment became non-significant after 7.3 h.[5]

In recent years, the role of the temporal window in the treatment of acute ischaemic stroke has been reduced and attention has been paid to the concept of brain tissue window. In particular, the therapeutic choice is tailored to the individual patient according to the extent of the mismatch between the volume of the ischaemic core, i.e. the area of the brain already undergoing necrosis, and the ischaemic penumbra, that is the hypoperfused area only reversibly damaged, that can benefit from urgent revascularization. The vascularization of the ischaemic penumbra depends on the extent of the leptomeningeal collateral circulation, which can determine its more or less rapid evolution towards necrosis. In fact, some patients who have a poor representation of the collateral circulation in multiphasic computed tomography (CT) angiography studies show a worse clinical outcome even if they are recanalized within 6 h, compared to patients with good collateral circulation who are recanalized beyond this time window.

In an analysis of patients with anterior circulation stroke, treated with endovascular therapy up to 12 h after the onset of symptoms, enrolled in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study, the authors found a correlation between the amount of the collateral circulation, baseline NIHSS score, and volume of the ischaemic penumbra. Better collateral circulation corresponded to lower NIHSS score and a greater volume of ischaemic penumbra assessed by perfusion magnetic resonance imaging (MRI). In this case, out of 60 patients, 65.5% who had good collateral circulation achieved an optimal reperfusion (defined as 2b-3 score on the thrombolysis in cerebral infarction—TICI scale), compared to only 29% of patients with poor collateral circulation. No difference in clinical outcome was found between the two groups with good recanalization. On the contrary, in patients who did not achieve an optimal recanalization (TICI score 0–2a), the clinical outcome was worse if the collateral circulation was poor.[6] The presence of collateral vessels is related to a greater degree of recanalization and in turn with a better clinical outcome. A recent subanalysis of the DEFUSE-3 study, on the other hand, found, against all expectations, that the degree of the collateral circulation was not predictive of the patient's functional independence and of the effect of EVT, whereas it was associated with a lower volume of the ischaemic core and its reduced growth.[7]

The progressive development and the greater availability of advanced imaging radiological techniques [multiphase angio-CT, perfusion-CT and MRI with diffusion-weighted imaging (DWI), FLAIR and perfusion-weighted imaging (PWI) sequences] allowed to define parameters identifying the ischaemic core and the penumbra and to quantify, also through the use of automated software (RAPID®), the presence of core/penumbra mismatch, and therefore of tissue that can be saved from irreversible ischaemic damage through reperfusion therapies. The Defuse-3 and Dawn trials have made it possible to extend the indication to the EVT of acute stroke up to 24 h from the last time the patient was known to be well, by selecting it on the basis of the presence of mismatch in RM DWI and PWI or in CTP[8,9] (*Figure 1*).

Recently, the Hermes study group analysed individual patients data from seven trials about mechanical thrombectomy MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE, in particular the clinical outcome and safety parameters, according to the characteristics of baseline neuroimaging. ASPECT score, thrombus density and volume (through the Clot burden scale), collateral circulation extent, ischaemic volume greater or lower than 33% of the territory of the middle cerebral artery were evaluated, and a benefit of mechanical revascularization was found also in groups of patients who are known to be associated with unfavourable clinical outcomes or futile recanalization. A good clinical outcome, evaluated with the mRS scale, was found in the treated group compared to the control group also in patients with ASPECT score <4 and in patients with an infarct involving more than 33% of the territory of the middle cerebral artery [adjusted common odds ratio (cOR) 2.00, 95% confidence interval (CI) 1.69–2.38; $P < 0.0001$]. The benefit was not found only in the category of patients with ASPECT score 0–2. There were no significant differences in mortality at 90 days and in the development of type 2 intraparenchymal haematoma 5 days after treatment, between the group of the treated patients and the controls. A higher rate of symptomatic intracranial haemorrhage (sICH) (defined as a clinical worsening expressed by an increase of at least 4 points on the NIHSS scale) was reported among patients undergoing EVT with an ASPECT score 0–4 (19% vs. 5%, adjusted cOR 3.94, 95% CI 0.94–16.49; *P*-interaction $= 0.025$) and with infarct involving more than 33% of the territory of the middle cerebral artery (14% vs. 4%, adjusted cOR 4.17, 1, 30–13.44, *P*-interaction $= 0.012$). These data confirm the efficacy of the treatment even in patients with large lesion volumes.[10] Currently, the American Heart Association/American Stroke Association (AHA/ASA) guidelines suggest with recommendation Class I, level of evidence A, to perform CT angiography and MRI angiography for the selection of patients undergoing mechanical thrombectomy with an ASPECT score between 6 and 10. In patients with an ASPECT score <6 it might be useful to perform advanced neuroimaging with perfusion study, but this data must be confirmed by randomized trials.[1]

A sub-analysis of the SELECT (Optimizing Patient's Selection for Endovascular Treatment in Acute Ischaemic Stroke Study) study compared the combined treatment with EVT and IVT vs. isolated medical therapy in patients with large ischaemic core, defined as an ASPECT score <6 or a volume of the ischaemic core $>50\,cm^3$; almost all patients had a $>20\%$ mismatch. Among 105 patients, those undergoing EVT had better clinical outcome at 90 days (mRS 0–2) than those undergoing only medical therapy (31% vs. 14%, OR 3.27, 95% CI 1.11–9.62; $P = 0.03$). No patient with an ischaemic core $>100\,cm^3$ achieved functional independence. Unlike the patients selected in the DEFUSE 3 and DAWN trials, in patients with large ischaemic cores, time would have a predominant role in the probability of achieving a good clinical outcome, becoming non-significant for treatments performed beyond 12 h. Further

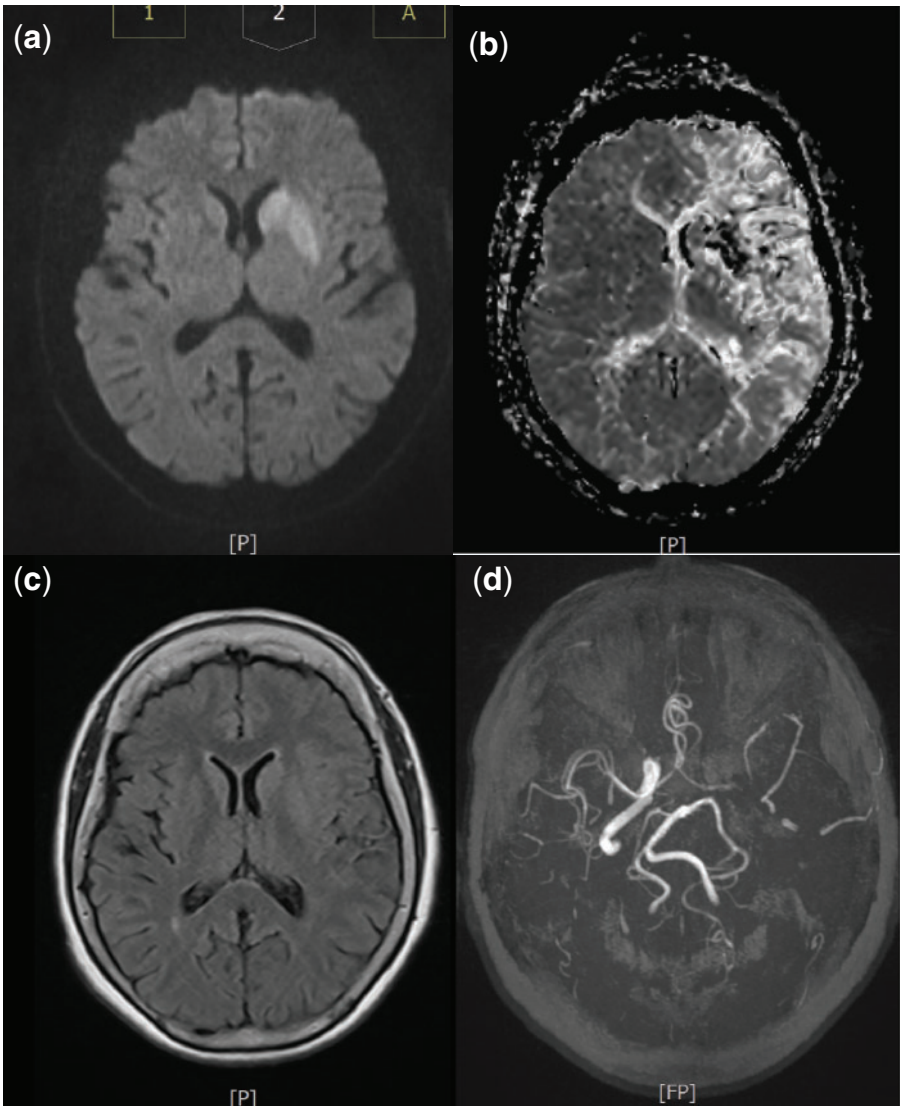

Figure 1 Patient with wake up stroke. MRI performed on baseline shows acute ischaemic lesion with wide mismatch between DWI (*A*) and PWI (*B*) sequences. The ischaemic lesion is absent on FLAIR sequence (*C*). MRI angiography shows tandem occlusion of left internal carotid artery and left middle cerebral artery. The patient underwent mechanical thrombectomy.

trials are ongoing to define the benefit of treatment in this category of patients (TENSION, IN EXTREMIS).[11]

As regards systemic thrombolysis treatment, data have recently been published concerning the possibility of treatment beyond the canonical 4.5-h window. First of all, the WAKE UP trial, which enrolled patients with unknown onset of symptoms, selecting them based on the presence of a mismatch between the DWI and FLAIR images, indicating a likely onset of symptoms within 4.5 hours. A favourable 90-day clinical outcome (defined as an mRS score 0–1) was demonstrated in 53.3% of patients treated with alteplase compared to 41.8% of those treated with placebo [adjusted odds ratio (aOR) 1.61, 95% CI 1.09–2.36; *P* 0.02]. However, it should be noted that in this trial 89% of the patients awoke from sleeping with stroke symptoms, and that the average value of the NIHSS was 6 (mild–moderate stroke). The incidence of symptomatic haemorrhagic transformation in the group treated with rtPA was 2%,[12] similar to that obtained in patients treated within 4.5 h.

The EPITHET, EXTEND, and ECASS IV-ExTEND trials evaluated the possibility of extending thrombolytic treatment to patients with onset beyond 4.5 h.

The EPITHET study enrolled patients treated between 4.5 and 6 h on the basis of baseline CT, but MRI was also performed and DWI/PWI mismatch evaluated after treatment and correlated with clinical outcome. Alteplase treatment was associated with higher reperfusion rates and better clinical outcome. In particular, an excellent clinical outcome (defined by mRS score 0–1 at 3 months) was found in 15% of cases, in particular among patients with mismatch than in those without mismatch, even if the difference was not statistically significant. There was no statistically significant difference between the two groups in terms of mortality.

The EXTEND study selected patients with ischaemic stroke that occurred between 4.5 and 9 h and with ischaemic penumbra highlighted by MRI DWI/PWI. Compared to the WAKE UP trial, only 65% of patients had stroke on

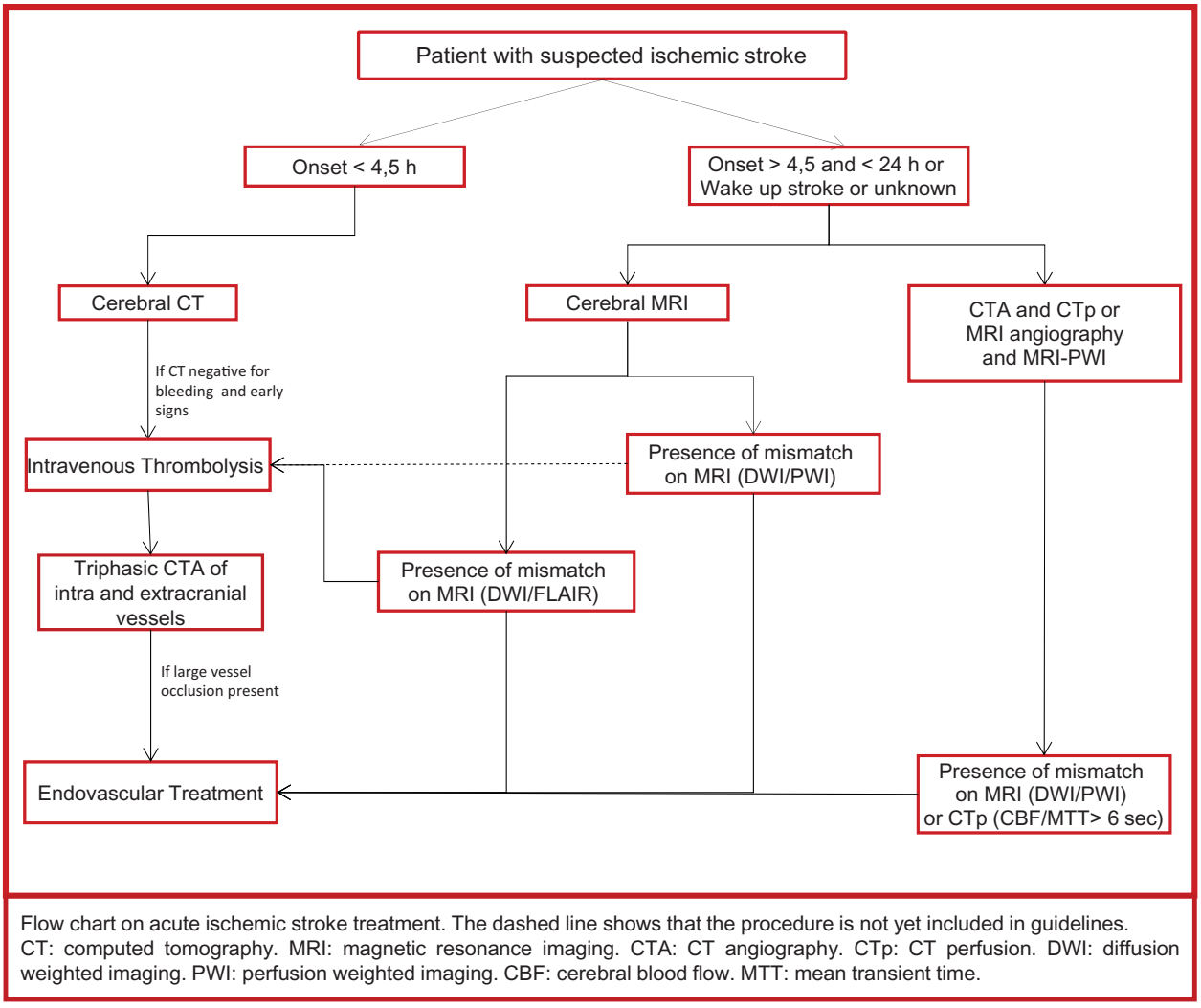

Figure 2 Flow chart on acute ischaemic stroke treatment. The dashed line shows that the procedure is not yet included in guidelines. CBF, cerebral blood flow; CT, computed tomography; CTA, CT angiography; CTp, CT perfusion; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; MTT, mean transient time; PWI, perfusion weighted imaging.

waking. The primary goal of mRS 0–1 at 90 days was achieved in 35.9% of patients treated with alteplase and in 29.5% of those treated with placebo (cOR 1.44; 95% CI 1.01–2.06; *P* 0.04). The not-corrected OR did not show statistical significance. Alteplase treatment resulted in a reperfusion rate of at least 50% in 71.7% of patients after thrombolysis, compared to 52.3% in the placebo group. The sICH rate was 6.2% of the treated group compared to 0.9% of the placebo group.[13]

The ECASS IV-Extend study selected patients with onset between 4.5 and 9 h with DWI/PWI mismatch evidenced by MRI perfusion images (ratio of 1.2) and minimum lesion volume of 20 mL, and randomized them to alteplase or placebo. The average time between onset of symptoms and administration of thrombolysis was 7 h and 42 min. There were no significant differences in terms of 90-day clinical outcome, assessed with mRS, between the two groups (OR 1.20; *P* 0.58), nor in terms of 90-day mortality.[14]

A meta-analysis based on the individual data of the 414 patients enrolled in the ECASS IV, EXTEND, and EPITHET trials showed that 36% of the patients treated with alteplase achieved an mRS score 0–1 at 3 months against 29% of the patients treated with placebo (aOR 1.86, 95% CI 1.15–2.99; *P* 0.011). The sICH rate was 5% in the alteplase group vs. <1% of placebo patients (aOR 9.7, 95% CI 1.23–76.55; *P* 0.031), and 3-month mortality was 14% and 9%, respectively (aOR 1.55, 95% CI 0.81–2.96; *P* 0.66). The benefit of treatment in this category of patients was achieved, and it was statistically significant if the selection was performed with automated perfusion mismatch calculation techniques.[15]

The algorithm of recanalization therapies for acute ischaemic stroke is represented in the flow chart.

Interesting data also derive from trials that compared the use of tenecteplase (TNK) with that of alteplase in patients with LVO and candidates for EVT. Compared to alteplase, the TNK led to a restoration of the flow in more than 50% of the territory involved by ischaemia or to a complete disappearance of the thrombus at the time of diagnostic angiography in 22% of cases, compared to 10%

achieved with alteplase (12% incidence difference; $P = 0.002$ for non-inferiority; $P = 0.03$ for superiority). The method of administration of the drug in a single bolus would make it particularly useful in patients who must be transferred to a HUB centre for EVT. But at the moment there is no indication to replace alteplase with TNK, because the superiority of the latter has not yet been demonstrated in improving the clinical outcome of patients.

Conclusions

Reperfusion therapies are the cornerstone of acute ischaemic stroke therapy and must be administered as soon as possible from the onset of symptoms to ensure greater efficacy of treatment. Research has made huge strides in providing the best treatment to an increasing number of patients. The individualized patient selection based on the extent of the ischaemic penumbra and the extent of the leptomeningeal collateral circulation allowed us to overcome the limits imposed by the rigid time windows, defining a benefit of mechanical revascularization therapies up to 24 h from the last time the patient was known to be well. This indication is already present in the AHA/ASA guidelines and will soon be implemented by the new Italian ISO-SPREAD guidelines. The extension of the therapeutic window for systemic thrombolysis up to 9 h from the onset of symptoms requires confirmation from the real world. Recent meta-analyses have attempted to re-evaluate the indication for treatment in patients with high ischaemic volume and randomized trials are currently underway. Promising studies on IVT with TNK could change the prognosis of patients with LVO who arrive in Primary Stroke Center (PSC), not equipped with interventional neuroradiology service, and therefore need to be transferred to a II level centre.

Advanced neuroimaging methods with perfusion studies are fundamental tools in patient selection. Their spread in the territory, together with a greater availability of neurovascular treatment units are desirable to ensure a fair delivery of treatment to all patients with ischaemic stroke.

Conflict of interest: none declared.

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