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Intravenous thrombolysis and intra-arterial interventions in acute ischemic stroke: Italian Stroke Organisation (ISO)-SPREAD guidelines

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Introduction

i.v. Thrombolysis (IVT) is the most important achievement of the last 20 years in the field of ischemic stroke management. In Italy, the evidence that stroke units were effective per sé in improving stroke outcome was not sufficient to favor their implementation. Only the approval of IVT boosted the activation of stroke units, which are now 170 centers widespread over the country. The numbers of treatments, however, are still limited, amounting in 2014 to approximately 4200 out of the 10 000 which should theoretically be performed each year. Too strict exclusion criteria and/or their too restrictive interpretation are two of the main causes of this substantial undertreatment. Hence, a critical reappraisal of these criteria was necessary.

On the other hand, recent evidences on the potentialities of intra-arterial interventions made it mandatory to better define the role of these techniques in the chain of treatments for acute ischemic stroke.

A panel of vascular neurologists (D. T., D. I., A. C., E. A., P. C., A. Z.) and of interventional neuro-radiologists (S. M., S.V., M. B.) collected the data through a systematic review of the available literature, searching electronic databases including PubMed, EMBase, OVID, and Cochrane Library, up to May 2015. Reference lists of the selected articles were also scrutinized. Each panelist was assigned individual sections, then the panel assessed the complete guidelines.

Recommendations were formulated by integrating the principles of the Scottish Intercollegiate Guideline Network with the statistical considerations suggested by the Centre for Evidence-Based Medicine methodology (Table 1). When literature data and practice experience data were not available or not considered to be sufficient, no specific recommendation was made. Consensus was reached during face-to-face discussions. In case of disagreement, a majority decision was taken.

Recommendations were then revised by a larger group of experts pertaining to the fields of trial methodology, vascular neurology, cardiology, emergency medicine, neurosurgery, vascular surgery, neuro-radiology, and rehabilitation (see Appendix S1), which in particular checked for the congruence between the grading and the source data.

Background information from literature

In the first part of the paper, we will revise data from RCTs, meta-analyses, and registries on IVT and i.a. interventions. Then, we will consider also data from cohort studies, case-control studies, and case reports and will formulate the recommendation.

Intravenous thrombolysis

The randomized controlled trials (RCTs) with recombinant tissue plasminogen activator (rt-PA) NINDS (1), ECASS (2), ECASS II (3), ATLANTIS (4), and their pooled analysis (5) showed a clear correlation between stroke onset to treatment interval and efficacy of intravenous (i.v.) thrombolysis, while parenchymal hematoma type 2 (PH2) was correlated with the treatment and with age, but not with the time interval between stroke onset and treatment (5).

Basing on this data, in September 2002, the European Medicines Agency (EMA) gave conditional approval for use of rt-PA.

The condition was that treatment was carried out only in the context of the post-marketing observational study Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) and that at the same time, a new randomized placebo-controlled trial in the therapeutic window of 3–4.5 hours, named ECASS III, was run in selected centers.

The SITS-MOST study treated 6483 patients in 14 European countries. Symptomatic intracerebral hemorrhage (sICH), defined as a clinical worsening of at least 1 point on the NIHSS scale in the presence of any type of intracerebral bleeding, was observed in 7.3% (95% CI 6.7–7.9) of patients, compared with 8.6% (95% CI 6.3–11.6) in previous RCTs; Three-month mortality was 11.3% (95% CI 10.5–12.1) compared with 17.3% (95% CI 14.1–21.1) in RCTs, and functional independence at threemonths was achieved by 54.8% of patients (95% CI 53.5–56.0) compared with 49.0% (95% CI 44.4–53.6) in RCTs (6).

Final approval of rt-PA within three-hours of onset of ischemic stroke was released by EMA in 2006 and implemented by the Agenzia Italiana del Farmaco (AIFA) in 2007.

The ECASS III trial randomized 820 patients to i.v. rt-PA or placebo between 3 and 4.5 hours after symptom onset. SICH, defined as above, occurred in 7.9% of rt-PA and in 3.5% of placebo patients (OR 2.38, 95% CI 1.25–4.52), three-month mortality was respectively 7.7% and 8.4% (OR 0.90, 95% CI 0.54–1.49) of cases, and functional recovery (mRS 0–1) was achieved respectively by 52.4% and 45.2% of patients [adjusted OR (aOR) 1.42, 95% CI 1.02–1.98] (7).

At the same time, the SITS International Stroke Registry (SITSISTR) compared the clinical outcome of 664 patients receiving i.v. rt-PA between 3 and 4.5 hours with that of 11 865 patients treated within three-hours. SICH was seen in 8.0% of patients treated between 3 and 4.5 hours and in 7.3% of those treated within

three-hours (aOR 1.13, 95% CI 0.97–1.32), mortality rate was respectively 12.7% and 12.2% (aOR 1.15, 95% CI 1.00–1.33), and functional independence was achieved respectively by 58.0% and 56.3% of patients (aOR 0.93, 95% CI 0.84–1.03) (8).

The combination of this data finally led to the approval of the extension to 4.5 hours of the therapeutic window for i.v. rt-PA in November 2010 by the EMA and in October 2013 by the AIFA.

Independently from the EMA requirements, the International Stroke Trial 3 (IST 3) (9) basing on the uncertainty principle randomized 3035 ischemic stroke patients to rt-PA or control within six-hours of the onset of symptoms, regardless of age or severity. Overall, 53% of patients were aged >80 years, and 95% did not meet the criteria of the EMA license for use of rt-PA. At six-months, 37% of treated patients and 35% of controls were alive and independent (OR 1.13, 95% CI 0.95–1.35). Ordinal analysis showed a benefit of 27% for patients treated with rt-PA (common OR 1.27, 95% CI 1.10–1.47). Intracerebral hemorrhage occurred in 7% of patients in the treatment group compared with 1% among control patients. Mortality at six-months was 27% in both groups. Patients aged over eighty and those with more severe neurological deficits benefited from treatment, which proved particularly good for those treated within three-hours.

Finally, the pooled analysis of individual data of 6756 patients from nine randomized trials with rt-PA vs. control (10) showed that rt-PA significantly increased the odds of a good outcome (mRS 0–1 at three- to six-months) among patients treated within 4.5 hours, with earlier treatment associated with greater proportional benefits (delay ≤3 hours: OR 1.75, 95% CI 1.35–2.27; delay 3–4.5 hours: OR 1.26, 95% CI 1.05–1.51; delay >4.5 hours: OR 1.15, 95% CI 0.95–1.40). Older age did not shorten the time window during which rt-PA could effectively be given ($P = 0.08$).

There was no evidence that rt-PA was proportionally less effective in those with the least or most severe strokes. Rt-PA significantly increased the odds of sICH (PH2 definition: 6.8% vs. 1.3%, OR 5.55, 95% CI 4.01–7.70) and of fatal ICH within seven-days (2.7% vs. 0.4%, OR 7.14, 95% CI 3.98–12.79), irrespective of treatment delay, age, or stroke severity, though the absolute excess risk increased with increasing stroke severity. There was no excess in other early causes of death and no significant effect on later causes of death, and by 90 days, mortality was similar in both groups (HR 1.11, 95% CI 0.99–1.25).

Intra-arterial treatments

Intra-arterial thrombolysis was investigated in patients with middle cerebral artery occlusion (MCA) in three small RCTs, using recombinant pro-urokinase (11,12) or urokinase (13). The meta-analysis of the three trials (14), for a total of 334 randomized patients within six-hours of onset of symptoms, showed a significant reduction of death/disability at three-months (58.8% vs. 69.2%, OR 0.58, 95% CI 0.36–0.93), and a risk of sICH at 24 h of 10% with pro-urokinase and 9% with urokinase. Intra-arterial thrombolysis has not been approved by either the FDA or the EMA, given the lack of confirmation from a larger trial.

In patients with intra-cranial arterial occlusions (carotid terminus, MCA tracts 1 or 2, vertebral or basilar arteries), ineligible for or poorly responding to IVT, different systems have been used for mechanically removing the thrombus in open-label, nonrandomized studies with a therapeutic window up to eight-hours.

Studies with the MERCI (15), multiMERCi (16), and PENUMBRA (17) systems reported recanalization rates of 46% (15) to 82% (17) with intraprocedural complications and secondary bleeding varying from 6% (16) to 13% (17), mortality rate between 34% (16) and 37% (17), and clear correlation between successful recanalization and favorable clinical outcome.

Two noninferiority randomized trials compared the MERCI system with the stent retriever SOLITAIRE (18) and with the TREVO system (19). The SWIFT trial reported a recanalization rate of 24% with the MERCI system, compared with 61% with SOLITAIRE (18), while the TREVO trial gave a 60% recanalization rate with the MERCI system and 86% with TREVO (19). Also in these trials, the higher rate of recanalization corresponded to a higher percentage of favorable clinical outcome (58% with SOLITAIRE vs. 33% MERCI (18) and 40% with TREVO vs. 22% with MERCI (19)).

All these studies were nonrandomized and used a broad therapeutic window, assuming that nonpharmacological intervention would permit a reduction of the risk of secondary hemorrhage, but contrary to the notion of the limited duration of survival of brain tissue in penumbra.

In March 2013, the results of three RCTs were published which evaluated the efficacy and safety of intra-arterial treatments with the gold standard of IVT.

The SYNTHESIS Expansion (20) trial randomized 362 ischemic stroke patients within 4.5 hours of symptom onset between intra-arterial treatment (intra-arterial thrombolysis with rt-PA or mechanical removal of the thrombus or a combination of the two approaches) ($N = 181$) or IVT with rt-PA ($N = 181$). Median time interval between onset of symptoms and treatment was 3.45 hours for intra-arterial treatment and 2.45 hours for IVT ($P < 0.001$).

At three-months, 30.4% of patients undergone intra-arterial treatment, and 34.8% of those receiving IVT had a favorable clinical outcome (aOR 0.71, 95% CI 0.44–1.14). Fatal or nonfatal ICH within seven-days occurred in 6% of patients in both groups.

The IMS III trial (21) randomized patients who had started IVT with rt-PA within three-hours of symptom onset to receive intra-arterial treatment (bridging) or to complete IVT in a ratio of 2 : 1. The trial was stopped prematurely after an interim analysis performed on 656 patients (434 in the bridging arm and 222 in the IVT arm), which showed a favorable clinical outcome (mRS 0–2) at three-months in 40.8% of the bridging patients and 38.7% of those receiving IVT (adjusted absolute difference 1.5%, 95% CI – 6.1–9.1). Clinical outcome did not differ also in predefined subgroups of patients with baseline NIHSS score 8–19 (difference – 1.0%, 95% CI –10.8–8.8) or ≥ 20 (difference 6.8%, 95% CI –4.4– 18.1). Three-month mortality was similar between the two groups (19.1% in the bridging arm and 21.6% in IVT arm), as well as the incidence of sICH (6.2% and 5.9%, respectively).

The MR RESCUE (22) trial randomized 118 patients with anterior circulation ischemic stroke to receive mechanical thrombectomy with MERCI or PENUMBRA device or standard treatment within eight-hours of the event (on average about 40% of patients in all arms received IVT). All patients underwent CT or MRI before treatment, and randomization was stratified according to the presence of a favorable ischemic penumbra (small infarct core and a substantial amount of salvageable brain tissue) or an unfavorable one (extended core infarct, small or absent penumbra) found in 58% and 42% of patients, respectively.

Patients without penumbra had the worst clinical outcome, whatever the treatment. Among patients with penumbra, three month mortality of those who underwent intra-arterial treatment was similar to that of patients receiving standard treatment (18% vs. 21%), as was the incidence of sICH (9% vs. 6%) or favorable clinical outcome (14% vs. 23%). Slow recruitment rates, with quite a few number of patients treated per center per year and a probable nonconsecutive recruitment, and the failure to demonstrate an arterial occlusion at the time of randomization (20,21) are some limitations of these trials.

Technical limitations were the use of mechanical thrombus removal systems in only one-third of patients in the SYNTHESIS Expansion (20) trial or the use in the IMS III and MR RESCUE trials of the MERCI (21,22) or PENUMBRA (22) systems, whereas at least the first of these two systems had proven less effective compared with stent retriever systems (18,19). Despite this, the rate of partial or complete recanalization achieved in the IMS III trial ranged from 81% in case of occlusion of the carotid artery, to 86% in MCA1 occlusions, to 88% in MCA2 occlusions (21), while in the MR RESCUE trial, it was on average 67% (22).

Futile recanalization (23), likely consequent to the on average long time interval between symptom onset and arterial reopening, is a plausible explanation of the poor clinical efficacy.

More recently, publication of five other trials have shed new light on the issue of mechanical thrombectomy.

The MR CLEAN (24) trial investigated safety and effectiveness of intra-arterial treatment, associated or not to mechanical thrombectomy, in 500 ischemic stroke patients. NIHSS ≥ 2 , occlusion of ICA terminus, MCA 1 or 2 or ACA 1 or 2, documented with CTA, MRA or DSA, and the possibility to start intra-arterial treatment within six-hours of onset were the main inclusion criteria.

The study included patients receiving IVT ($N = 455$) and patients not treated with IVT ($N = 55$) due to contraindications to i.v. t-PA or because overcoming the 4.5 hours therapeutic window. Thrombectomy was performed with stent retriever devices (82%) but also first-generation devices, like MERCI and PENUMBRA. At the end of the study, despite broad entry criteria, enrolled patients had mainly MCA and ICA occlusions (92%) and rather severe strokes (median NIHSS 18). Patients treated with intra-arterial approach had three-month better clinical outcome: at ordinal analysis, adjusted common OR 1.67; 95% CI 1.21–2.30; at dichotomization mRS 0–2 32.6% vs. 19.1%, aOR 2.16; 95% CI 1.39–3.38. The incidence of sICH was 6% in treatment group and 5.2% in control patients. The subgroup analyses confirmed the effectiveness of intra-arterial treatment according to the stratification for age and site of occlusion and in patients with more severe baseline NIHSS score. Non intra-arterial treatment of 37 of the 233 patients randomized to intervention, of whom 16 due to clinical improvement ($N = 8$) or no clot visible at DSA ($N = 8$), would deserve further analysis of per-protocol treatments. The ESCAPE trial (25) randomized patients with a CTA confirmed intracranial proximal occlusion in the anterior circulation (carotid T or MCA, M1 or M2 segment), baseline NIHSS > 5 , good collaterals on multiphase CTA, CT-ASPECT score > 5 , and treatable < 12 hours, to standard care (control) or standard care plus endovascular treatment with available thrombectomy devices. About 79% of control patients and 73% of thrombectomy patients received i.v. rt-PA within 4.5 hours of stroke onset and before randomization, and although any thrombectomy device was allowed, in practice, newer generation retrievable stent devices were used. The trial was prematurely halted after randomization of 316 of 500 planned patients due to a positive interim analysis. At ordinal analysis, adjusted common OR was 3.1 (95% CI 2.0–4.7), while a mRS 0–2 at 90 days was reported in 53.0% in thrombectomy vs. 29.3% in controls (aOR 1.7, 95% CI 1.2–2.2).

Reduction of mortality was significant (10.4% vs. 19.0% in the control group, $P = 0.04$), and sICH was observed in 3.6% intervention vs. 2.7% control patients (adjusted rate ratio 1.2, 95% CI 0.3–4.6). Subgroup analysis according to age, sex, baseline NIHSS, site of occlusion, baseline ASPECT score, previous treatment with i.v. t-PA confirmed the results in all subgroups, including the elderly. The study was not powered to assess endovascular therapy among the 49 participants presenting 6–12 h of symptom onset.

The EXTEND-IA trial (26) was a phase II trial looking at a combined tissue and clinical end point (early reperfusion and neurological improvement on day 3), which randomized patients with CTA or MRA occlusion of intracranial carotid or MCA M1 or M2 segments, limited ischemic core and significant mismatch at MR- or CT perfusion (using the RAPID® software) and treatable < 6 hours. All patients had to be treated with IVT < 4.5 hours of stroke onset. Endovascular therapy had to be initiated within six-hours after stroke onset and completed within eight-hours after onset.

The trial was prematurely stopped because of a positive interim analysis after the first 70 of 100 planned patients. Early reperfusion of the ischemic tissue at 24 h with thrombectomy with the Solitaire™ FR stent retriever was 100% vs. 37% in the control group (aOR 4.7, 95% CI 2.5–9.0; $P < 0.001$), and early neurological improvement (i.e. NIHSS reduction ≥ 8 points or NIHSS 0–1 at three-days) was observed in 80% of intervention vs. 37% in control group (aOR 6.0, 95% CI 2.0–18; $P < 0.002$). Three-month mRS 0–2 was reported in 71% of thrombectomy patients and 40% in controls (aOR 4.2; 95% CI 1.4–12, $P < 0.01$), and mortality respectively in 9% and 20% of patients (aOR 0.45; 95% CI 0.1–2.1). sICH was detected in 6% of control patients and in no thrombectomy patient. The early trial termination may create potential for overestimation of the effect size. Moreover, of the 35 patients allocated in the endovascular group, four (11.4%) had the majority of the thrombus already lysed before angiography, and additional four (11.4%) did not undergo thrombectomy for various reasons.

The SWIFT-PRIME trial (27) randomized patients aged 18–80 years, who were receiving or had received i.v. t-PA to continue with t-PA alone (control patients) or to be submitted to mechanical thrombectomy with stent retriever (intervention patients)

within six-hours of stroke onset. Patients had to have proximal anterior intracranial circulation occlusion (intracranial carotid or MCA M1 or M2 segments), ASPECT score ≥ 6 at CT or DW MR, and baseline NIHSS score ≥ 8 and < 30 . The initial one-third of patients were randomized in case of limited ischemic core with significant mismatch at MR or CT perfusion (using the RAPID® software). The trial was halted after an interim analysis on 196 of the planned 750 patients. Thrombectomy plus i.v. t-PA reduced 90-day disability over the entire range of mRS scores ($P < 0.001$).

Three-month mRS 0–2 was achieved by 60% of intervention and 35% of control patients (OR 1.70; 95% CI 1.23–2.33, $P < 0.001$). No significant differences in 90-day mortality (9% intervention vs. 12% control, $P = 0.50$) and sICH (0% vs. 3%, $P = 0.12$) were detected. Subgroup analysis confirmed the results irrespective of age, sex, baseline NIHSS, and site of occlusion.

The REVASCAT trial (28) randomized patients aged 18–80 years, with proximal anterior intracranial circulation occlusion, baseline NIHSS score ≥ 6 , and no large ischemic core (ASPECT score ≥ 7 at CT or ≥ 6 at DW MR), to medical therapy and endovascular therapy (thrombectomy group) or medical therapy alone (control group). In all patients, i.v. t-PA either did not achieve revascularization or was contraindicated. The trial was halted after enrollment of 206 of the planned 1068 patients. Thrombectomy reduced the severity of disability over the range of mRS (aOR for improvement of 1 point 1.7; 95% CI 1.05–2.8), and 90-day mRS 0–2 was reported in 43.7% and 28.2% of patients, respectively (aOR 2.1, 95% CI 1.1–4.0). Three-month mortality was 18.4% in intervention patients and 15.5% in control patients ($P = 0.60$), while sICH was 1.9% in both groups ($P = 1.00$).

All these trials evidence consistently efficacy and safety of mechanical thrombectomy, mainly when given after i.v. t-PA.

Since the median interval times between onset of i.v. t-PA and groin puncture range from 51 (23) to 152 min (28), very likely most patients received complete i.v. t-PA infusion before thrombectomy, and therefore, procedures seem to consist at large with the ‘rescue’, rather than with the ‘bridging’ approach.

Higher reperfusion rates and frequency of functional independence were obtained in the ESCAPE (25), EXTEND-IA (26), and SWIFT-PRIME (27) trials, partially explainable with earlier start of the intervention (25–27) and fewer intracranial (27) or cervical (25–27) occlusions of the internal carotid artery. Moreover, in the ESCAPE (25) and EXTEND-IA (26) trials and partially in the SWIFT-PRIME trial (27), selective operational and advanced diagnostic procedures were used to exclude from treatment patients with large core infarcts. These procedures are far from being available in any common stroke centre worldwide, and their applicability likely deserves more testing before recommendations become largely generalizable.

Extra-cranial carotid artery occlusion

Tandem extracranial ICA occlusion was reported in 32.2% of patients in the MR CLEAN trial (24), 12.7% in the ESCAPE trial (25), and 18.6% in the REVASCAT trial (28), with favorable effect of thrombectomy.

A systematic review (29) of case series of patients with occlusion of the extra-cranial internal carotid artery treated with IVT ($N = 338$) or with intra-arterial procedures ($N = 193$) has evidenced that favorable clinical outcome (43.5% vs. 26.3%, OR 0.46, 95% CI 0.32–0.68) but also sICH (11.4% vs. 3.9%, OR 0.31, 95% CI 0.15–0.63) was less frequent among patients receiving IVT. Mortality rate was instead similar for both groups (26.4% vs. 27.2%, OR 1.041, 95% CI 0.7–1.56).

In a more recent systematic review of studies on intra-arterial thrombolysis or any type of thrombectomy in patients with extraand/or intra-cranial ICA occlusion (30), the population with extracranial ICA occlusion treated with stenting had higher recanalization rate (87% vs. 48%, $P = 0.001$), favorable outcome rate (68% vs. 15%, $P < 0.001$), and lower mortality (18% vs. 41%, $P = 0.048$) than patients treated with i.a. thrombolysis. In the tandem occlusion population, death rate was significantly lower in the group treated with i.a. thrombolysis when compared with the groups receiving any mechanical treatment of the intracranial occlusion (0% vs. 34%, $P = 0.002$ and 0% vs. 33%, $P = 0.001$).

The comparisons, however, were not randomized, and studies were very heterogeneous, so resulting evidence has to be considered frail.

Basilar artery occlusion

No data from RCTs are currently available for patients with basilar artery occlusion. A meta-analysis of 45 studies, for a total of 2056 patients, showed that basilar artery recanalization with IVT or intra-arterial/endovascular therapy (IA/EVT) was associated with a lower risk of death or dependency (overall RR 0.67; 0.68 in IVT subgroup and 0.67 in IA/EVT subgroup) and mortality (overall RR 0.49; 0.53 in the IVT subgroup, 0.48 in the IA/EVT subgroup).

With IVT, the ICH rate was 9%, and with IA/EVT, the ICH rate was 14% (31).

The BASICS registry (32) did not demonstrate the superiority of endovascular treatments compared with IVT. The BASICS trial is now ongoing (33), comparing thrombectomy within six-hours in addition to IVT to IVT alone performed within 4.5 hours of stroke onset.

Indications for treatment

Intravenous thrombolysis

The inclusion criteria and the absolute exclusion criteria for IVT are shown in Tables 2 and 3.

With regard to age, the current RCP of Actilyse® gives an upper age limit of 80 years old. However, according to RCTs (9,10), an upper age limit is no longer justified.

Some exclusion criteria for the use of Actilyse®, shown in Table 4, are not evidence based but were introduced by EMA putatively to maximize safety of the treatment.

The experience accumulated over the years by centers performing IVT suggests that use of the drug is effective and sufficiently safe regardless the presence of these ‘relative’ exclusion criteria.

Data reported in literature may be useful for providing accurate information to the patient and/or family on the risks and benefits of off-label treatment in presence of these criteria.

Mild deficit of rapid improvement of symptoms

Up to 25% of patients excluded from thrombolysis because of mild neurological deficits may later deteriorate with unfavorable

outcome (34). In RCTs, patients presenting with mild deficits (NIHSS < 5) benefit from IVT (10).

For the same reason, rapid improvement should be regarded as a criterion for exclusion from treatment only if it leads to an NIHSS score of 0, since as long as there is still a measurable deficit, an indication for IVT persists. Notably, IVT of patients with mild stroke is basically safe (35).

Unknown time of onset or stroke present upon awakening

For patients having unwitnessed stroke, the last time the patient was seen or heard in normal conditions is usually taken as the time of symptom onset. In case of stroke on awakening, the time of onset is by convention considered the time when the patient went to sleep.

Due to these conventional definitions of time of onset, both these types of patients are very frequently outside the therapeutic window of 4-5 hours.

However, diffusion-weighted (DW)/perfusion-weighted (PW) MR 'mismatch' (i.e. small infarct core in DW, compared with a much larger area of hypoperfusion in PW) may give an indication for treatment (36,37). Similar information can be obtained with perfusion CT (pCT).

In addition, the lack of any hyperintensity or subtle hyperintensity on MR FLAIR within the area that appears damaged in the DW sequences may be considered indicative of a symptom onset within three-hours (38).

IVT has been proved safe and effective even in a series of patients with stroke on awakening and no early signs of ischemia on CT or involving <1/3 of the MCA territory (39).

Seizure at stroke onset

IVT may be administered to patients presenting with seizures at onset of symptoms (40) when there is clinical evidence that the deficit is not a postcritical one but is related to cerebral ischemia.

If necessary, clinical suspicion may be supported by MR DW imaging, pCT, or CT angiography (41,42).

Patients with history of stroke and concomitant diabetes

A case-control study of 29 500 patients from the SITS-ISTR register (cases treated with IVT) compared with patients in the Virtual International Stroke Trials Archive register (control stroke patients not receiving IVT) showed that patients with history of previous stroke and concomitant diabetes receiving thrombolysis, despite a mild nonstatistically significant increase in mortality, had a better functional outcome (aOR 1.23, 95% CI 0.996–1.52) than nonthrombolysed controls (43).

Serum glucose levels <50 or >400 mg/dl

Serum glucose values <50 mg/dl require immediate correction to exclude that hypoglycemia is responsible for focal neurological signs mimicking a stroke.

If the neurological disorder persists after hypoglycemia correction, IVT may be performed within 4-5 hours of symptom onset.

In case of doubtful diagnosis, MR DW/PW sequences or pCT may be helpful.

If serum glucose is >400 mg/dl, blood sugar must be reduced with s.c. or i.v. insulin administration. If serum glucose levels fall below 200 mg/dl within 4-5 hours of onset of symptoms, IVT may be performed.

History of stroke in the last three-months

The scarce data available do not indicate a significant increase in the risk of worse clinical outcome, or bleeding complications in the part of the brain affected by the first stroke (44,45). The decision to treat should be made on a case-by-case basis taking into account: the size and time of the first stroke (higher risk of hemorrhage for larger, more recent lesions), patient age (risk of bleeding potentially increasing with age and risks/benefits ratio as a function of life expectancy), and potential severity of the new event (also definable using MR DW/PW or pCT).

Uncontrolled severe arterial hypertension

Uncontrolled severe hypertension is defined as systolic blood pressure (SBP) >185 mmHg or diastolic blood pressure (DBP) >110 mmHg, or requiring aggressive therapy to bring the blood pressure within these limits.

IVT may be administered once SBP is <185 and DBP <110.

These values must be maintained during treatment and in the 24 h after thrombolysis.

Clinically severe stroke (e.g. NIHSS > 25) and/or severe according to appropriate neuro imaging techniques

In RCTs (10), clinically severe patients (NIHSS ≥ 22) benefit from IVT.

The IST trial (9) showed that even in the presence of early signs of ischemia on brain CT, the benefit of IVT remains.

However, caution should be taken in cases with very extensive early signs (>1/3 of the MCA territory or ASPECT score <7), in which the risks/benefits of treatment should be scrutinized in individual patient.

Patients with basilar artery occlusion may present with severe conditions (quadriplegia or coma) but may benefit from IVT (31).

Patients on oral anticoagulant treatment with AVK drug and INR ≤ 1.7

A comparison of 768 patients on warfarin therapy with INR ≤ 1.7 at the time of treatment with i.v. rt-PA with 44 306 patients not on oral anticoagulant therapy prior to IVT showed that prior anticoagulant therapy with INR ≤ 1.7 did not increase the risk of sICH (ECASS definition aOR 1.26, 95% CI 0.82–1.70) or mortality (aOR 1.05, 95% CI 0.83–1.35), and did not influence clinical outcome (aOR 1.01, 95% CI 0.81–1.24) (46).

Patients on direct anticoagulant treatment (thrombin or Xa-factor inhibitor)

Thus far, 27 case reports have been published on patients submitted to i.v. thrombolysis while on direct oral anticoagulant (DOAC) therapy: 17 on dabigatran, nine on Rivaroxaban, and one on apixaban. SICH was reported in two patients receiving dabigatran.

In particular, one patient received thrombolysis six-hours after the last of three doses of dabigatran and was per se at risk of bleeding, since he was diabetic with baseline blood glucose of 233 mg/dl and had a large cardioembolic stroke with hypoperfusion at PW-MR involving the entire MCA territory. Specific tests were reported in four patients on dabigatran and in four patients on rivaroxaban, while aPTT or PT were performed in the majority of patients and were normal in 40–60% of cases in which the reference ranges are reported (47).

Despite the very limited and anecdotal evidence, IVT may be considered for patients treated with DOACs basing on clinical history (dose and time interval since the last intake, renal function, liver function, concomitant therapy with P-glycoprotein inhibitors) and on specific standardized tests (diluted thrombin time, ecarin clotting time, or Hemoclot for dabigatran, anti-Xa calibrated for rivaroxaban or apixaban) (48,49).

Patients on anticoagulant treatment with low molecular weight heparin

In a multicenter prospective study of 1482 patients receiving IVT, 21 (1.4%) were treated with low molecular weight heparin (LMWH) before stroke, five of which at therapeutic doses ($\geq 60 \text{ mg} \times 2$) for acute deep vein thrombosis or pulmonary embolism or systemic embolism prophylaxis and 16 at low doses (40 mg daily) for prevention of deep vein thrombosis.

The time interval between the last dose of LMWH and administration of alteplase was < 6 hours in one patient, < 12 h in two cases, and < 24 h in 18 cases.

Compared with those not treated with prior anticoagulant therapy, these patients had a higher risk of sICH (OR 8.42, 95% CI 2.20–32.23) and of mortality (OR 5.3, 95% CI 1.8–15.5), with a lower likelihood of a favorable clinical outcome (OR 0.3, 95% CI 0.1–0.97) (50).

Overall, the limited data available do not permit to estimate the relationship between various doses of LMWH, timing of administration, and risk of bleeding after IVT.

Hence, whether or not treating these patients must be decided case by case, taking into account the risks/benefits calculated on the basis of available data and the expected patient prognosis in the absence of thrombolysis.

Patient on single or dual antiplatelet treatment

Antiplatelet treatment prior to stroke is not an exclusion criterion for IVT, but the inherent possible risk of bleeding is worth being discussed here.

Studies aimed at identifying predictors of sICH after IVT have given conflicting results on the possible role of a single antiplatelet therapy, while the role of dual antiplatelet treatment appears more significant (51).

However, in the IST 3 (9), trial patients with a history of antiplatelet treatment benefited from IVT (ordinal analysis: OR 1.20, 95% CI 0.87–1.65).

Hence, it is advisable to inform the patient on antiplatelet therapy of the increased risk of bleeding with IVT.

History of CNS diseases: cancer, brain or spine surgery

The few data available in literature do not show a higher risk of worse clinical outcome or bleeding complications in patients treated with IVT and CNS diseases including operations for subdural hematoma or cerebral contusion ($N = 8$), or for meningiomas ($N = 3$) or shunts for normal pressure hydrocephalus ($N = 2$) (52), or the concomitance of tumors such as meningiomas ($N = 4$), cholesteatomas ($N = 1$), acoustic schwannomas ($N = 1$), or paranasal tumors ($N = 1$) (52–54).

Arterial aneurysm

In a retrospective analysis of 236 patients receiving IVT, 22 (9.3%) had an unruptured cerebral aneurysm. Post-thrombolysis cerebral hemorrhage occurred in 14% of patients with aneurysms compared with 19% of those without aneurysms, and sICH occurred in none of the former and 5% of the latter (55).

Arteriovenous malformation

Patients with arteriovenous malformations treated with IVT are too sporadic in literature (56,57) to be able to express an opinion. In these patients, one can consider the option of primary intraarterial treatment (see below).

History of intracranial hemorrhage (parenchymal or subarachnoid)

Literature reports three cases of patients with a past medical history of subarachnoid or parenchymal hemorrhage who underwent IVT (52), with no bleeding complications and in two cases with a favorable functional outcome.

In these cases, it is essential to assess the risks/benefits of thrombolysis, taking into account potential risk conditions such as the presence of micro-bleedings, severe leukoaraiosis, or amyloid angiopathy, clearly detectable using multimodal MR.

Pregnancy

A systematic review of 172 pregnant women treated with thrombolytic agents for various thromboembolic disease reported bleeding complications in 8% of cases (58). Literature reports data on nine patients with stroke in pregnancy treated with IVT, most of which in the first or second trimester and one in the third trimester of pregnancy (59). The fetal outcome was good in six cases, while two pregnant women had minor hemorrhagic events (one intracerebral hemorrhage and one uterine hemorrhage), and one patient died for arterial dissection during subsequent angioplasty (60,61). Rt-PA is a large molecule and does not cross the placenta, so it should not have teratogenic effects. It can however act on the placenta with the potential risk of premature labor, placenta detachment, or fetal death (61).

It is recommended to discuss risks/benefits of the treatment for the patient and fetus.

Thrombolysis and menstruation

Active bleeding is a contraindication for thrombolytic treatment.

However, the limited data available in literature (30 patients) show that rt-PA may be safely administered in menstruating women (62). Bleeding may increase and may require blood transfusion (reported to be necessary in only two out of the 30 patients treated). This may occur particularly at the beginning of menstruation or if the woman has a history of dysmenorrhea. Hence, the patient has to be informed, and possible transfusion should be considered.

Major surgery or major trauma

Case series of patients with acute ischemic stroke and recent (within 14 days according to the AHA guidelines, within threemonths according to the EMA) major surgery (e.g. inguinal hernia, resection of ovarian cancer, coronary artery or femoropopliteal bypass, bowel resection, splenectomy, uvulectomy) or noncranial major trauma (e.g. fracture of femur, upper limb, knee) treated off-label (52,53,63) suggest the possibility of administering IVT.

In these cases consider whether primary mechanical intraarterial treatment might be appropriate.

Cranio-cervical arterial dissection

Cranio-cervical arterial dissection (CAD) is not an exclusion criteria for IVT mentioned in the summary of product characteristics of alteplase but may be seen as such by less experienced clinicians. A metanalysis of individual patient data from retrospective series or case reports (64) reported the outcome of 180 patients with craniocervical dissection (carotid artery $n = 131$, basilar artery $n = 48$, both arteries $n = 1$) treated with i.v. ($N = 121$) or i.a. ($N = 59$) thrombolysis. Of the 121 patients receiving IVT, 58.2% had three-month mRS 0–2, 3.3% had sICH, and 7.3% died, as opposed respectively to 52.2%, 3.0%, and 8.8% of 170 patients with stroke from all causes treated with IVT and matched for age and stroke severity.

Hence, IVT should not be denied to patients presenting with ischemic stroke due to CAD

Recommendations	Grade
Treatment with i.v. rt-PA (0.9 mg/kg, maximum dose 90 mg, 10% of the dose as bolus, the remainder in 60 min infusion) is recommended within 4.5 hours of onset of ischemic stroke, without upper limits of age and severity. However, treatment must be carried out as early as possible.	A
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with mild deficits or rapidly improving symptoms which are however still detectable at the time of starting treatment.	B
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with a history of prior stroke and diabetes.	B
Treatment with i.v. rt-PA is recommended in patients with unwitnessed stroke or stroke present on awakening, when advanced neuro-imaging (DW/PW MR or pCT) define an area of tissue mismatch and/or enable dating of the event within at least three-hours (compare DW with FLAIR MR).	D
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with focal neurological deficit onset with seizure, when there is clinical evidence, if necessary supported by neuro-imaging (DW/PW MR or PCT), that the residual neurological deficit is not a post-critical deficit but is attributable to a cerebral ischemia.	GPP
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with blood glucose <50 mg/dl and neurological deficit which persists after the restoration of normal blood glucose.	GPP
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with blood glucose > 400 mg/dl if, treated with s.c. or i.v. insulin, it drops below 200 mg/dl.	GPP
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with a history of stroke over the last three-months taking into account: the extension of the previous lesion and time interval since the first stroke (higher risk of hemorrhage for larger and more recent lesions), patient age (potential increased risk of bleeding with older age and risk/benefit ratio as a function of life expectancy), potential severity of the new event (also definable by means of neuro-imaging techniques such as MR DW/PW or pCT).	GPP
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients with severe arterial hypertension after reaching the pressure range SBP < 185 and DBP < 110, which must be maintained during treatment and for 24 h after thrombolysis.	GPP
Treatment with i.v. rt-PA within 4.5 hours of symptom onset is recommended in patients on oral anticoagulant treatment with vitamin K antagonists and INR ≤ 1.7.	GPP

Intra-arterial treatments Intra-arterial treatment subsequent to IVT

Intra-arterial pharmacological thrombolysis does not offer advantages over IVT (20).

The various techniques of mechanical thrombectomy, possibly aided by the use of thrombolytic or antiplatelet drugs, achieve high rates of recanalization.

As already mentioned, their superiority in terms of efficacy and safety compared with IVT has not yet been evidenced (20–22), while their use after IVT in patients with ICA terminus, MCA1–2, or ACA 1–2 occlusion was effective and safe (24–28).

Hence, patients with these arterial occlusions, documented by transcranial Doppler or CTA or MRA, with/without concomitant occlusion of extra cranial internal carotid artery, are eligible for intra-arterial treatment within six-hours of stroke onset. According to evidences from trials, i.v. t-PA infusion should be completed, but start of thrombectomy should not be delayed.

The same procedure is likely applicable to patients with vertebral artery, basilar artery, or PCA occlusion.

To select patients to be investigated for arterial occlusion, an NIHSS score ≥ 9 within three-hours of stroke onset (65,66) and ≥ 7 between three- and six-hours (65) of onset can be used.

Intra-arterial treatments in case of absolute criteria for exclusion from IVT

The MR CLEAN (24), ESCAPE (25), and REVASCAT (28) trials included globally 188 patients (108 intervention and 80 control patients) who could not be treated with IVT. As there is a lack of strong evidence from RCTs in this area, suggestions are based on the clinical experience and on low-quality evidence as case control studies and case series, and the inclusion in RCTs should be the first option offered to the patients whenever possible.

In the presence of some of the exclusion criteria for IVT indicated in Table 5, a primary intra-arterial option may be considered.

Stroke onset >4.5 hours

In patients with stroke onset of over 4.5 hours, the intra-arterial option should preferably be completed within a maximum of six-hours of onset of symptoms, which means starting the procedure possibly within five-hours of onset.

If procedure start is expected to exceed five-hours from the onset of symptoms, mismatch on the MRI DW-PW or pCT should be documented.

In the presence of occlusion of distal arterial branches not treatable with mechanical devices, intra-arterial administration of thrombolytic agents may be considered.

Recent major surgery or major trauma

In patients with acute ischemic stroke and recent major surgery or recent noncranial major trauma (<14 days according to the AHA guidelines, <3 months according to the EMA), after clinical assessment and evaluation of the risk of bleeding, intra-arterial treatment may be considered (63).

Patients on oral anticoagulant treatment with AVK drugs and INR > 1.7

In these patients, intra-arterial treatment is possible (67) after evaluation of the risks/benefits of the procedure.

Patients on direct anticoagulant treatment (thrombin or Xa-factor inhibitor)

To date, five cases of stroke patients taking DOACs (three on dabigatran, two on rivaroxaban) and treated with mechanical thrombectomy have been published (68–71). In all patients, aPTT and/or PT was in the normal range. Patients achieving recanalization within 5–30 hours of onset of symptoms had a favorable outcome (68–70). One patient on rivaroxaban was recanalized after eight-hours of stroke onset and had an unfavorable outcome (68). In no case sICH was reported.

Patients on anticoagulant treatment with LMWH

There is no data in literature on the outcome of patients treated with LMWHs before the stroke and submitted to intra-arterial treatment.

However, whenever possible, it is reasonable to consider a primary mechanical intra-arterial treatment.

Remaining criteria

For the remaining exclusion criteria for IVT such as neoplasm with increased bleeding risk; severe liver disease, including liver failure, cirrhosis, portal hypertension (esophageal varices), active hepatitis; hemorrhagic retinopathy; increased bleeding risk for comorbidities; recent (<10 days) traumatic external heart massage, childbirth, puncture of noncompressible blood vessel (e.g. subclavian or jugular); and ulcer disease of the gastrointestinal tract (<3months), there are no data in literature on effects of intra-arterial treatments.

However, it is reasonable to individually consider the risks/benefits of intra-arterial mechanical intervention which as such entails a limited risk of bleeding.

Recommendations	Grade
In patients eligible for IVT, intra-arterial reperfusion treatments are not recommended as an alternative.	A
The techniques of mechanical thrombectomy are recommended within six-hours of stroke onset in patients with occlusion of ICA terminus, middle cerebral artery M1–M2, or anterior cerebral artery A1 who do not respond to or cannot be treated with IVT.	B
The techniques of mechanical thrombectomy are recommended within six-hours of stroke onset in patients with occlusion of vertebral artery, basilar artery, or posterior cerebral artery P1 who do not respond to or cannot be treated with IVT.	GPP

Table 1 Levels of evidence and grades of recommendations

Levels of evidence	Grades of recommendations
1++ High-quality meta-analysis without heterogeneity; systematic reviews of RCTs each with small CIs; or RCTs with very small CIs and very small α and β	A: At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population
1+ Well-conducted meta-analyses without clinically relevant heterogeneity; systematic reviews of RCTs; or RCTs with small CIs and/or small α and β	A: Systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
1– Meta-analyses with clinically relevant heterogeneity; systematic reviews of RCTs with large CIs; or RCTs with large CIs and/or α and β	B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
2++ High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with very small CIs and very small α and β	
2+ Well conducted case-control or cohort studies with small CIs and/or small α and β	C: A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
2– Case-control or cohort studies with large CIs and/or α and β	
3 Nonanalytic studies (i.e. case reports or case series)	D: Evidence level 3 or 4; or extrapolated from studies rated as 2+; or evidence from trials classified as – regardless of the level
4 Expert opinion	
– Meta-analyses with clinically relevant heterogeneity; systematic reviews of trials with large CIs; trials with large CIs and/or α and/or β	GPP: recommended best practice based on the clinical experience of the guideline development group, without research evidence

Table 2 i.v. Thrombolysis: inclusion criteria

Patients of both sexes aged ≥ 18 years
Ischemic stroke responsible for a measurable language, motor, cognitive, visual perception deficit, and/or neglect
Onset of symptoms within 4-5 hours (at administration of rt-PA)
Symptoms present for at least 30 min. Symptoms should be distinguished from those of an episode of generalized ischemia (i.e. syncope), seizure, or migraine crisis
Patients (or family members) must have received treatment information and have given consent to the use of their data and to follow-up procedures

Table 3 i.v. Thrombolysis: absolute exclusion criteria

Stroke onset $>4-5$ hours
Intracranial hemorrhage on brain CT
Clinical suspicion of SAH, despite normal CT
Administration of i.v. heparin in the previous 48 h and aPTT above laboratory normal upper limit
Platelet count $<100\ 000/\text{mm}^3$
Known hemorrhagic diathesis
Current or recent severe bleeding
Suspected intracranial hemorrhage
Bacterial endocarditis, pericarditis
Acute pancreatitis
Neoplasm with increased hemorrhagic risk
Severe liver disease, including liver failure, cirrhosis, portal hypertension (esophageal varices), active hepatitis
Hemorrhagic retinopathy (e.g. changes in vision in diabetics)
Increased hemorrhagic risk due to comorbidity
Recent (<10 days) traumatic external heart massage, childbirth, puncture of noncompressible blood vessel (e.g. subclavian or jugular vein)
Ulcer disease of the gastrointestinal tract (<3 months)

Table 4 i.v. Thrombolysis: relative exclusion criteria*

Mild deficit or rapidly improving symptoms (30 min)
Unknown time of onset or stroke present on awakening
Seizure at stroke onset
Patient with a history of stroke and concomitant diabetes
Blood glucose <50 or >400 mg/dl
History of stroke in the last three-months
Uncontrolled severe arterial hypertension
Clinically severe stroke (e.g. NIHSS > 25) and/or severe according to appropriate neuro-imaging techniques
Patient on oral anticoagulant treatment
Patient on anticoagulant treatment with low molecular weight heparins
History of CNS diseases: cancer, brain or spine surgery, aneurysm
History of intracranial hemorrhage (parenchymal or subarachnoid)
Pregnancy
Major surgery or severe trauma (<3 months)

*Reported in the summary of product characteristics of Actilyse but contradicted or not supported by literature.