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Review article

UPDATE IN THE MANAGEMENT OF ACUTE ISCHEMIC STROKE

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Abstract

Acute ischemic stroke (AIS) occurs due to a sudden thrombotic or embolic occlusion of a cerebral artery, which results in impaired neurologic function. The data from the World Health Organization (WHO) show that 15 million people suffer a stroke worldwide each year. Of these, 5 million have lethal outcome, and another 5 million have permanent disability. Stroke is the second most common single cause of mortality in Europe. According to the system of stroke classification developed in the multicenter Trial of ORG 10172 in Acute Stroke Treatment (TOAST), ischemic stroke is divided into the following 3 major subtypes: large-artery, small-vessel, or lacunar and cardioembolic infarction. Diagnosis of AIS is established based on a neurological examination, computer tomography (CT), scans or magnetic resonance imaging (MRI) scans, Doppler ultrasound, and CT/MR angiography. The main pillars of AIS treatment are stroke unit (SU) care and treatments promoting revascularization. Since 2002, intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) has been approved in Europe for use in acute stroke treatment. In the beginning of 2021, the European Stroke Organization (ESO) published new guidelines on intravenous thrombolysis for AIS. There are 40 new recommendations and the most important ones focus on early and late time windows, stroke of unknown onset, advanced imaging, use of alteplase and tenecteplase, minor and severe strokes, intravenous thrombolysis in patients over 80 years of age or with previous disability or frailty and potential risk factors for bleeding including use of oral anticoagulants.

Keywords: acute ischemic stroke, management, guidelines, intravenous thrombolysis, mechanical thrombectomy

Definition. Acute ischemic stroke (AIS) occurs due to a sudden thrombotic or embolic occlusion of a cerebral artery, which results in impaired neurologic function.

Epidemiology. The data from the World Health Organization (WHO) show that 15 million people suffer stroke worldwide each year. Of these, 5 million have lethal outcome, and another 5 million have permanent disability[1]. Stroke is the second most common single cause of mortality in Europe. It is responsible for more than 1 million deaths every year and is the leading cause of long-term disability. Approximately 20- 35% of stroke patients die within the first month after a stroke, and 1/3 of the stroke survivors lose their independence. The socioeconomic impact of stroke is considerable: the annual cost of stroke in Europe is estimated to be €45 billion: €20 billion for direct care, €9 billion related to loss of productivity and €16 billion for informal care. The burden of stroke differs widely across Europe, the incidence and case fatality

of stroke in central and eastern European countries remain higher than in northern, western and southern European countries[2, 3].

Etiology. According to the system of stroke classification developed in the multicenter Trial of ORG 10172 in Acute Stroke Treatment (TOAST), ischemic stroke is divided into the following 3 major subtypes: large-artery, small-vessel, or lacunar and cardioembolic infarction[4]. Large-artery strokes occur due to local thrombotic occlusions in the carotid, vertebrobasilar, and intracranial arteries, but they can also be cardioembolic. Cardioembolic strokes account for up to 20% of acute strokes, cause more severe neurological deficit, tend to have more frequent hemorrhagic transformation and have the highest 1-month mortality[5]. Small vessel or lacunar strokes are associated with small focal areas of ischemia due to occlusion of single small vessels, typically in deep penetrating arteries. In many patients the exact etiology of their stroke is not identified and these are classified as cryptogenic strokes. A subset of cryptogenic stroke is embolic stroke of undetermined source (ESUS), defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources[6].

There are certain risk factors for ischemic stroke that include modifiable and nonmodifiable conditions. Nonmodifiable risk factors include age, race, gender, ethnicity, history of migraine headaches, fibromuscular dysplasia and genetic factors[7]. Modifiable risk factors are: hypertension (the most frequent), diabetes mellitus, cardiac disease, hypercholesterolemia, obesity, carotid stenosis, hyperhomocysteinemia, alcoholism, smoking, illicit drug use, physical inactivity, oral contraceptive use/postmenopausal hormone use and sickle cell disease[8].

Diagnosis. Diagnosis of AIS is established based on a neurological examination (such as the National Institute of Health Stroke Scale - NIHSS), computer tomography (CT) scans (most often without contrast enhancements) or magnetic resonance imaging (MRI) scans, Doppler ultrasound, and CT/MR angiography. Blood laboratory tests may be of help in finding out the likely cause of stroke[9].

Treatment. The main pillars of AIS treatment are stroke unit (SU) care and treatments promoting revascularization. SUs are defined as dedicated areas or wards in hospitals open round the clock, where stroke patients are admitted and cared for by a multidisciplinary team including medical, nursing and therapy staff, are most effective in reducing mortality and morbidity[10]. Since 2002, intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) has been approved in Europe for use in acute stroke treatment, given at a dosage of 0,9 mg/kgBW (maximum 90 mg, 10% of the dose in bolus, rest in IV infusion during 60 min.) in the period of 3-4,5 hours after symptom onset[11]. Recanalization strategies, i.v., recombinant tissue-type plasminogen activator (alteplase or rt-PA) attempt to establish revascularization cells within the ischemic penumbra (a metabolically active region, peripheral to the ischemic area, where blood flow is reduced and the cells are potentially viable) can be rescued before irreversible injury occurs[12]. Tissue in this area of oligemia can be preserved by restoring blood flow to the compromised area and optimizing collateral flow. Restoring blood flow can mitigate the effects of ischemia only if performed quickly.

In the beginning of 2021, the European Stroke Organization (ESO) published new guidelines on intravenous thrombolysis for AIS[13]. There are 40 new recommendations and the most important ones focus on early and late time windows, stroke of unknown onset, advanced imaging, use of alteplase and tenecteplase, minor and severe strokes, intravenous thrombolysis in patients over 80 years of age or with previous disability or frailty and potential risk factors for bleeding including use of oral anticoagulants. The new recommendations again confirm the use

of IVT in AIS with less than 4,5 hours duration, because it leads to better functional outcome than no IVT. For patients with AIS of 4.5–9 h duration (known onset time), and with no brain imaging other than plain CT, IVT is not recommended. For patients with IS of 4.5–9 h duration (known onset time) and with CT or MRI core/ perfusion mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, IVT with alteplase is recommended. For patients with AIS on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, IVT with alteplase is recommended. For patients with AIS on awakening from sleep, who have CT or MRI core/perfusion mismatch within 9 h from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, the experts recommend IVT with alteplase. For patients with AIS of <4.5 hours duration and not eligible for thrombectomy, IVT with alteplase over IVT with tenecteplase is suggested. For patients with AIS of < 4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom IVT is considered before thrombectomy, the experts suggest IVT with tenecteplase 0.25 mg/kg over IVT with alteplase 0.9 mg/kg. For patients with AIS of < 4.5 h duration, ultrasound augmentation is not recommended in patients receiving IVT. For patients with AIS of < 4.5h duration, who are over 80 years of age, IVT with alteplase is recommended. All group members who wrote the guidelines have stated that age alone should not be a limiting factor for IVT, even in other situations covered in the present guidelines (e.g. wake-up stroke; ischemic stroke of 4.5–9 h duration (known onset time) with CT or MRI core/perfusion mismatch; minor stroke with disabling symptoms). Also, patients with multimorbidity, frailty or prestroke disability who have AIS of < 4.5 h duration can be treated with IVT with alteplase. For patients with acute minor, disabling IS of < 4.5 h duration, IVT with alteplase is also recommended, but if the AIS is non-disabling, IVT is not recommended. If patients have acute minor non-disabling IS of < 4.5 h duration, and with proven large-vessel occlusion, there is insufficient evidence to make an evidence-based recommendation. For patients with AIS of < 4.5 h duration, and rapidly improving neurological signs, which are still disabling, there is also insufficient evidence to make a recommendation. For patients with clinically severe AIS of < 4.5 h duration, the experts recommend IVT with alteplase. For patients with AIS of < 4.5 h duration, and with severe stroke, defined by the extent of early ischemic changes on CT, it is suggested that IVT with alteplase be considered in selected cases, such as patients with severe stroke associated with extended radiological signs of infarction (early ischemic change of more than 1/3 of MCA territory or ASPECTS < 7 on plain CT). For patients with AIS of < 4.5 h duration, and with persistently increased systolic blood pressure >185 mmHg or diastolic blood pressure >110 mm Hg even after blood pressure lowering treatment, IVT is not recommended. For patients with AIS of < 4.5 h duration, and with systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg, which has subsequently been lowered to < 185 and < 110 mm Hg, IVT with alteplase is recommended. For patients with AIS of < 4.5 h duration, and with known prestroke hypertension, IVT with alteplase is also recommended. For patients with AIS of < 4.5 h duration, and with blood glucose levels above 22.2 mmol/L (400 mg/dL), the experts suggest IVT with alteplase. Also, IVT should not prevent the administration of insulin therapy in AIS patients with high blood glucose levels. For patients with AIS of < 4.5 h duration, and with known diabetes mellitus, IVT with alteplase is recommended. If the patients have used dual antiplatelet agents prior to the stroke, and experience AIS of < 4.5 h duration, IVT with alteplase is suggested. For patients with AIS of < 4.5 h duration, who use vitamin K antagonists and have INR 1.7, IVT with alteplase is recommended, but if the INR is >1.7 or

unknown, then no IVT is recommended. For patients with AIS of < 4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e. calibrated anti Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), IVT is not suggested. If those tests are available, i.e. patients have an anti-Xa activity < 0.5 U/ml (for factor Xa inhibitors) or thrombin time < 60 s (for direct thrombin inhibitors), there is insufficient evidence to make an evidence-based recommendation. For patients with AIS of < 4.5 h duration, who used dabigatran during the last 48 h before stroke onset, there is insufficient evidence to make a recommendation for or against the use of the combination of idarucizumab and IVT with alteplase over no IVT. The expert consensus statement is that for patients with AIS of < 4.5 h duration, who used dabigatran during the last 48 h before stroke onset, 8 of 9 group members suggested the combination of idarucizumab and IVT with alteplase over no IVT. For patients with AIS of < 4.5 h duration, who used factor Xa inhibitors during the last 48 h before stroke onset, 9 of 9 group members suggested against the combination of andexanet and IVT with alteplase over no IVT. For patients with AIS of < 4.5 h duration, and with known platelet count < 100 109 /L, IVT is suggested. For patients with AIS < 4.5 h duration, and with unknown platelet count before initiation of IVT and no reason to expect abnormal values, the experts recommend starting IVT with alteplase while waiting for lab tests results. For patients with AIS of < 4.5 h duration and with major surgery on a non-compressible site where bleeding is likely to lead to significant hemorrhage (e.g., abdomen, chest, skull, well-vascularized tissues, or large artery) during the preceding 14 days, IVT is not recommended. For patients with AIS of < 4.5 h duration, and a history of intracranial hemorrhage, there is insufficient evidence to make an evidence-based recommendation. For patients with AIS of < 4.5 h duration and with a history of intracranial hemorrhage, 8 of 9 members suggest IVT with alteplase in selected cases: if a long time has elapsed since the hemorrhage, or if there was a non-recurrent or treated underlying cause for the hemorrhage (e.g. trauma, subarachnoid hemorrhage with subsequent endovascular or surgical aneurysm removal, or use of specific antithrombotic medication). For patients with AIS of < 4.5 h duration, for whom cerebral microbleed burden is unknown or known to be low (e.g. < 10), the experts suggest IVT with alteplase. But if the cerebral microbleed burden has been previously reported to be high (e.g. >10), the experts suggest no IVT. For patients with AIS of < 4.5 h duration, and small to moderate or high burden of white matter lesions, IVT with alteplase is recommended. For patients with AIS of < 4.5 h duration, who have an unruptured cerebral artery aneurysm, the experts suggest IVT with alteplase. For patients with AIS of < 4.5 h duration, and with a history of ischemic stroke during the last three months, there is insufficient evidence to make an evidence-based recommendation. For patients with AIS of < 4.5 h duration, and a history of ischemic stroke within the last three months, nine of nine members voted for IVT with alteplase in selected cases, for example in case of a small infarct, stroke occurring more than one month earlier, or good clinical recovery. For patients with AIS of < 4.5h duration who have seizures at the time of stroke onset, and in whom there is no suspicion of a stroke mimic or significant head trauma, the experts suggest IVT with alteplase. For patients with AIS of < 4.5 h duration and with aortic arch dissection, no IVT is recommended. For patients with AIS of < 4.5 h duration and with isolated cervical artery dissections, IVT with alteplase is suggested. For patients with AIS of < 4.5 h duration and with intracerebral artery dissections, there is insufficient evidence to make a recommendation. For patients with AIS of < 4.5 h duration and with history of subacute (>6 h) ST elevation myocardial infarction during the last seven days, the experts suggest no IVT. For patients with AIS of < 4.5 h duration and with history of ST-elevation myocardial infarction

of more than a week to 3 months, there is insufficient evidence to make a recommendation. For patients with AIS of < 4.5 h duration and with a history of non-ST-elevation myocardial infarction during the last three months, the experts suggest IVT with alteplase.

The Angels minimum criteria for a stroke ready hospital are the following:[14]

- 50 % of patients treated with iv rtPA in the time window door-to-needle <60 minutes
- 5-15% of recanalised/thrombolysed of all AIS
- 85% of neuroimaging CT or MRI in every suspected AIS
- 85% of ischemic strokes prescribed antithrombotic (antiaggregation) therapy at discharge
- 85% of anticoagulation therapy in AF patients at discharge
- 85% of patients with dysphagia screening

Several trials have confirmed the use of mechanical thrombectomy in patients with AIS[15].

ANGIO-CAT results showed that direct transfer of patients with suspected large vessel occlusion to the angiography suite saved time and improved outcomes at 3 months. AURORA trial findings strengthened the evidence for the benefit of endovascular thrombectomy across the 6-24 hour time window. BEST-MSU showed that more stroke patients could be treated in a shorter time and with improved outcomes, when their care occurred at a mobile stroke unit. MR CLEAN-NO IV showed that the benefit of transfer modality (drip and ship or mother ship) may depend on distance to the EVT center. Drip and ship may be better for patients with LVO that are candidates for iv-tPA or patients in remote areas. The SHRINE collaboration further documents the non-inferiority of primary thrombectomy versus combined therapy in patients with ischemic stroke due to proximal anterior circulation occlusions.

The overarching targets for 2030 from the Stroke Action Plan for Europe (SAP-E) are [16]:

1) Treat 90% or more of all stroke patients in Europe in a stroke unit as the first level of care.
2) Guarantee access to recanalisation therapies for 95% of all eligible stroke patients across Europe.
3) Decrease median onset-to-needle times to less than 120 min for intravenous thrombolysis and onset-to-reperfusion times to less than 200 minutes.
4) Achieve rates for intravenous thrombolysis above 15%, and for mechanical thrombectomy above 5% in all European countries.
5) Decrease first-month case-fatality to less than 25% for hemorrhagic stroke and increase rate of good clinical outcome to more than 50%.

Conclusion. It is crucial to understand that the results of any direct mechanical thrombectomy studies versus bridging IVT/mechanical thrombectomy studies only apply thrombectomy capable centers with fast mechanical thrombectomy workflow and immediate availability of a neurovascular team. In all other cases, IVT has to be provided to all eligible patients. There is always room for improvement, to shorten the onset-to-needle time, especially with the use of mobile stroke units.

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