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Recent advances in the acute management and long-term secondary prevention in transient ischaemic attack and ischaemic stroke

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ABSTRACT

Ischaemic stroke is by far the most frequent condition that neurologists routinely face in the hospital setting, accompanied by significant morbidity and long-term loss of function for the survivors. The approach of the potential stroke patient should start at the pre-hospital level, since time is of essence. Any focal neurological deficit of sudden onset should raise the suspicion of stroke or transient ischaemic attack (TIA), especially if no signs of seizures are present. After prompt brain imaging, in the setting of the emergency department, treatment mainly aims at reperfusing the tissue originally supplied by the occluded artery. This is achieved by either intravenous thrombolysis or mechanical thrombectomy. Certain criteria must be fulfilled in order to be able to apply these treatments. Moving away from the emergency approach, an important concern of the subacute (in-hospital) and long-term (post-hospitalisation) treatment of stroke patients surrounds the challenges regarding the proper use of antiplatelet and anticoagulant agents. The latter have a place in the long-term secondary prevention of cardioembolic stroke or TIA, while the former (either as a monotherapy or as a dual antiplatelet treatment) are mainly used in the management of the hospitalised patients and the secondary prevention of non-cardioembolic stroke and TIA.

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1. Introduction

Ischaemic stroke is by far the most frequent condition that neurologists routinely face in the hospital setting, accompanied by significant morbidity and long-term loss of function (i.e., significant drop in quality of life) for the survivors. Diagnosis and management of the condition nowadays follows internationally-acknowledged guidelines aiming at maximising the benefit for the patients, which depends on both the prompt and proper intervention of the paramedical and medical teams in the acute and subacute stage, as well as the best-fitting, long-term management of the patients. Prompt and proper intervention entails detection of patients with suspected stroke (ideally even before them reaching the emergency department, by the pre-hospital healthcare team) and guiding them timely through the proper diagnostic channels so as to confirm the diagnosis and the best therapeutic intervention (based on the type of ischaemic stroke and the temporal window). The best-fitting, long-term management of the patient relates to two main concerns: (i) identifying the underlying aetiology of the ischaemic stroke, that would assist in (ii) deciding on the most fitting treatment scheme for secondary prevention, taking also into consideration other parameters from the medical history of the patient (such as other co-morbid conditions and related drugs they may have to take). In this short paper, I will summarise the treatment options used at the acute, subacute, and chronic level of management of ischaemic stroke (Figure 1).

2. Approaching ischaemic stroke and transient ischaemic attack in the acute setting

Any focal neurological deficit of sudden onset should raise the suspicion of stroke or transient ischaemic attack (TIA), especially if no signs of seizures are present. The pattern of neurological semiology should guide clinical thinking on whether a potential lesion may originate from the brain (and not from the spinal cord or the peripheral nervous system), and subsequently, whether the potential stroke / TIA originates from the anterior circulation or the posterior circulation[1]. Additionally, patients should be promptly scheduled for brain imaging, with brain computed tomography (CT), CT angiography, and perfusion CT in order to (i) exclude the possibility of intracranial haemorrhage, (ii) capture evidence of lesion(s) compatible with an ischaemic stroke (although such evidence is usually absent at the acute stage), (iii) capture evidence of a large vessel occlusion (LVO), and (iv) estimate the extent of the potentially salvageable brain region (penumbra)[2]. In cases of TIA, patients should be classified as low- or high-risk (for future development of ischaemic stroke) based on the ABCD[2] scale. If the possibility of an ischaemic stroke cannot be excluded by the diagnostic approach in the emergency setting, the patient should be treated as such. The three main therapeutic concerns are to achieve timely recanalization of the occluded artery (i.e., reperfusion of the ischaemic tissue), optimise collateral flow, and avoid secondary brain injury.

Guidelines regarding the application of reperfusion treatments are available for adult patients (unfortunately there are limited data regarding paediatric stroke) and concern ischaemic stroke cases that either cause disabling symptoms (e.g. aphasia, hemianopia, or hemiparesis) or have a National Institutes of Health Stroke Scale (NIHSS) score above 4. Such patients are scheduled for mechanical thrombectomy, if there is evidence of LVO, and the treatment can be administered within 6 h of symptom onset. Patients with no evidence of LVO, are scheduled for intravenous thrombolysis if treatment can be administered within 4.5 h of symptom onset and no contraindications exist. Various trials are on-going in order to establish whether certain subgroups of patients may benefit from these reperfusion treatments, even if they do not fall within the aforementioned timeframes[3].

3. Basic principles of antiplatelet and anticoagulant use in the post-emergency stage of the ischaemic stroke

Moving away from the emergency approach of the stroke patient, an important concern of the subacute (in-hospital) and long-term (post-hospitalisation) treatment surrounds the challenges regarding the proper use of antiplatelet and anticoagulant agents. Generally, all ischaemic stroke patients are treated

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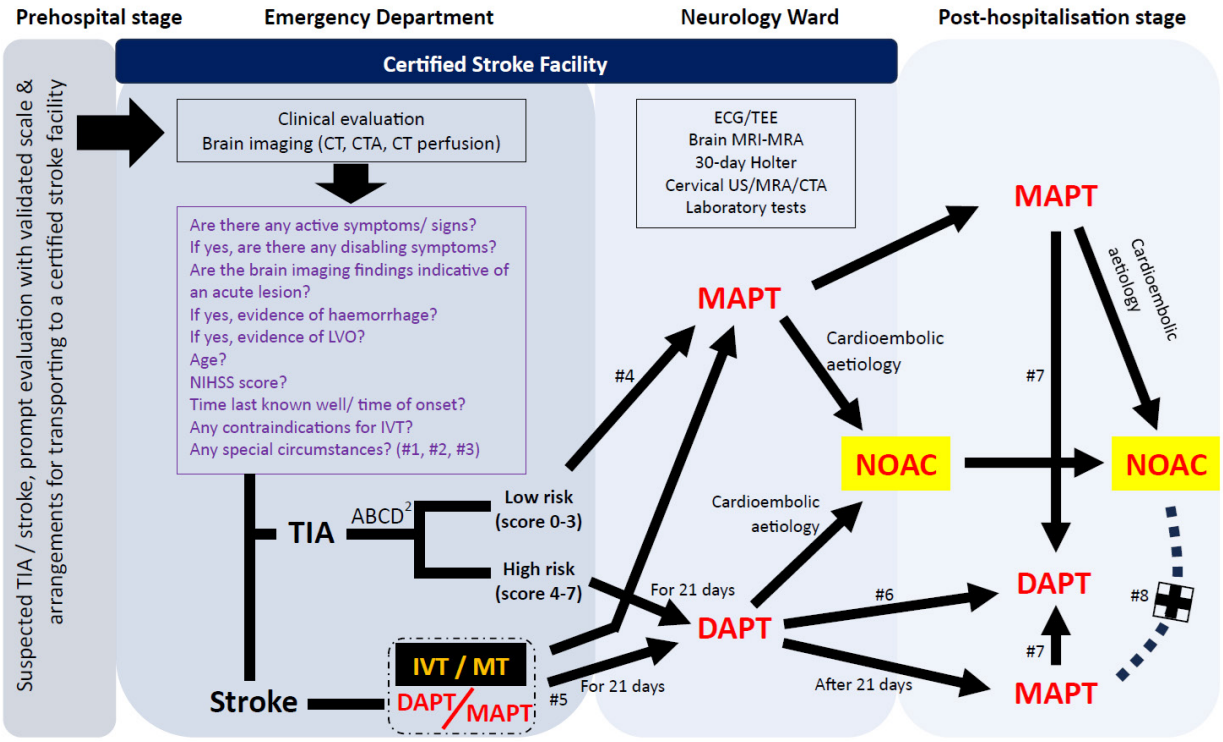

Figure 1. *Integrative management of TIA and ischaemic stroke. Approach of the patient with potential TIA / stroke should start at the prehospital level by the paramedical team responsible for promptly transporting the patient to a certified stroke facility. In the setting of the emergency department, stroke experts should evaluate the patient clinically and with brain imaging (CT, CTA, and perfusion CT). Based on this initial investigation, the patient will be categorised as suffering from a haemorrhagic stroke (outside the scope of this paper) or potentially TIA or ischaemic stroke. In suspected stroke, the age of the patient, the presence of disabling symptoms, the NIHSS score, any evidence of LVO, the presence of any contraindications of reperfusion treatment, and the time of the symptoms' onset will determine whether the patient is eligible for a reperfusion treatment (MT, IVT) or a conservative approach with immediate start of DAPT or MAPT in higher initial doses. The temporal window for IVT is 4.5 h after symptom onset. A subset of patients though might benefit from IVT even if conducted outside the 4.5 h window. These include wake-up strokes or strokes of unknown onset time with high diffusion-perfusion mismatch in MRI (up to 9 h) or, in cases of basilar artery occlusion, ineligible for MT, who do not have a large established pontine or cerebellar infarction, especially if they have fluctuating deficits (#1). The temporal window for MT is 6 h after the symptom onset. A subset of patients with LVO though might benefit from MT even if conducted outside the 6-h window. These include wake-up strokes or strokes of unknown onset time with high diffusion-perfusion mismatch in MRI (up to 24 h) (#2) or, in cases of basilar artery occlusion who do not have a large established pontine or cerebellar infarction, especially if they have fluctuating deficits (even >24 h) (#3). If no clinical or imaging evidence of ischaemic lesion is present, the symptoms of the patient have been completely resolved and the value of the ABCD² scale of the patient is below 4, then the patient can be considered as having experienced a low-risk TIA and can be discharged with instructions for undergoing further diagnostic evaluation (brain MRI, cervical US, ECG, 30-day Holter) and starting MAPT (and statin) (#4). If the ABCD² scale of the patient is above 3, then the patient is considered as having experienced a high-risk TIA, and the suggestion would be to be hospitalised, undergo the same diagnostic evaluation (in the hospital*

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setting), initiate DAPT (and statin) for 21 days, and switch to MAPT (and statin) after that period of time. DAPT is usually also administered for 21 days, instead of reperfusion treatment, in stroke cases with an NIHSS score <5 and non-disabling symptoms (#5). DAPT may exceed 21 days (it can go up to 90 days or even longer) in cases of extra- / intracranial major artery stenosis (#6). If the diagnostic approach reveals a cardioembolic origin of the TIA / stroke, antiplatelet treatment is converted to anticoagulant treatment (preferably NOAC). In cases of recurrent stroke of non-cardioembolic origin under MAPT, change in the long-term prevention strategy (from MAPT to DAPT) may be considered (#7). The addition of clopidogrel to the anticoagulant regime could potentially be useful for secondary prevention in cases of post-stroke patients who also display unstable coronary heart disease (angina) in the presence of atrial fibrillation (#8). Abbreviations used: ABCD^2, clinical scale to evaluate whether TIAs should be considered as low- or high-risk; CT, computed tomography; CTA, computed tomography angiography; DAPT, dual antiplatelet therapy; ECG, echocardiogram; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MAPT, antiplatelet monotherapy; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; TEE, trans-oesophageal echocardiogram; TIA, transient ischaemic attack; US, ultrasound.

in-hospital with an antiplatelet scheme independent of whether a reperfusion treatment was conducted at the acute stage, and are switched to an anticoagulant scheme if the diagnostic approach reveals a potential cardioembolic cause of the stroke. Another important question about the use of antiplatelet agents is whether a monotherapy (MAPT) or a dual antiplatelet therapy (DAPT) should be applied, and what its duration should be.

4. Antiplatelet agents and their use in the context of MAPT or DAPT

Various meta-analyses from multiple available randomised controlled trials have established that DAPT given within 24 h of a high-risk TIA or a non-cardioembolic mild stroke, for 21 days, can effectively reduce the risk of recurrent stroke and major adverse cardiovascular events compared to MAPT[4]. DAPT can be implemented in various occasions in the management of the ischaemic stroke patients: in the acute setting, DAPT can be used (instead of intravenous thrombolysis) in those patients that show no disabling symptoms, no evidence of LVO or capsular warning syndrome and have a NIHSS score below 6, while in the sub-acute setting, DAPT is indicated for 3 weeks in patients with an NIHSS score below 6 and for longer duration (90 days or even longer) in patients with symptomatic stenosis of carotid arteries. DAPT is not recommended as a long-term secondary prevention strategy, but may be considered for only very selected cases; these include: (i) recurrence of ischaemic stroke in patients under MAPT, when other preventive strategies have been unsuccessfully implemented (e.g., adherence to the MAPT has been ensured, no drug interactions exist that may render MAPT ineffective, investigation consistently revels no cardioembolic origin of the stroke, and variables such as arterial hypertension, diabetes mellitus, hypolipidemic treatment, and lifestyle have been tightly controlled for) and (ii) patients with non-valvular atrial fibrillation unsuitable for anticoagulant treatment[5].

MAPT is implemented in the remaining (and large majority) of ischaemic stroke and TIA cases; these include low-risk, non-cardioembolic TIAs, non-cardioembolic ischaemic strokes of greater severity (NIHSS score above 5) or disabling symptoms, following reperfusion treatment, or in the long-term, after the end of the DAPT period (usually 21 days) for secondary prevention.

Among the different types of antiplatelet agents that have been tested in randomised controlled clinical trials, aspirin (an irreversible cyclooxygenase inhibitor, which reduces platelet aggregation by inhibiting the synthesis of the procoagulant thromboxane A_2) and

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clopidogrel (a prodrug metabolised by the hepatic cytochrome P450 system to its active form, an irreversible inhibitor of the $P2Y_{12}$ class of adenosine diphosphate / ADP receptors on the surface of platelets, preventing ADP-mediated activation of the downstream glycoprotein IIb/IIIa complex, thereby resulting in reduced platelet aggregation) are those whose use has been widely established, either as MAPT or combination therapy (DAPT). Ticagrelor, with similar mode of action to clopidogrel, can replace the latter in the context of DAPT in cases of poor response to clopidogrel (usually due to reduced bioavailability in a subset of patients who possess loss of function polymorphisms in CYP2C19). Dipyridamole (with multiple modes of action, among which a cyclic adenosine monophosphate / cAMP-phosphodiesterase inhibitor, which also inhibits the reuptake and breakdown of adenosine by platelets, thereby enhancing prostaglandin I_2 biosynthesis) can also be used in the context of DAPT (with aspirin) for the secondary prevention of stroke in patients with recurrent stroke(s) under MAPT (either only aspirin or clopidogrel). Finally, cilostazol (a selective inhibitor of phosphodiesterase 3, which increases the activation of intracellular cAMP and, thereby, inhibits platelet aggregation and causes vasodilation) may have a role in the context of DAPT (with either aspirin or clopidogrel) in the long-term secondary prevention of stroke in patients with (extra- / intracranial) major artery stenosis either ≥50% or less significant but with 2+ additional risk factors (i.e., smoking, age ≥65 years, hypertension, diabetes mellitus, chronic kidney disease, recurrent stroke, ischaemic heart disease, peripheral vascular disease)[6].

5. Anticoagulant agents and their role in secondary prevention of stroke

Anticoagulant treatment (through the use of non-vitamin K antagonist oral anticoagulants or, rarely, vitamin K antagonists) has its place in the long-term secondary prevention after TIA or ischaemic stroke of cardioembolic origin. Its use can start as soon as 1 day after TIA, 4 days after a minor stroke (NIHSS score: <8), 7 days after a moderate stroke (NHISS score: 8–15), and 14 days after a severe one. In cases of haemorrhagic transformation or after mechanical thrombectomy, anticoagulant treatment can start after 4–14 or 5–14 days, respectively, following an individualised assessment of risks / benefits[7]. The aforementioned guidelines are not affected by the application of intravenous thrombolysis. There is only one case, where a combined antiplatelet (clopidogrel)-anticoagulant therapy may have benefits that outweigh the risks: this is the case of the long-term secondary prevention of recurrent stroke in patients who also suffer from unstable coronary heart disease (angina) in the presence of atrial fibrillation. However, more research is required on the topic.

6. Conclusion

Stroke constitutes the second cause of death worldwide, with a quarter of the cases being recurrent incidences. There have been significant advancements in the therapeutic approach and overall management of the condition over the last 2.5 decades. The approach of the potential stroke patient should start at the pre-hospital level, since time is of essence. In the acute setting, reperfusion treatment needs to be decided about. In the subacute, in-hospital setting antiplatelet treatment plays an important role, while in the chronic setting, stroke aetiology will dictate secondary prevention treatment (i.e., continuation of antiplatelet agents or switching to anticoagulant regimes).

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Conflicts of interest

None exist.

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