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Chapter

Diagnosis and Management of Acute Ischemic Stroke

Anwer Zohaib Siddiqi, Angela Young and Ankur Wadhwa

Abstract

This chapter will review updates in the various imaging modalities used to diagnose acute ischemic stroke (AIS), how these are used to select patients for intervention, and the different interventions used for management of AIS. The backbone of the AIS diagnostic algorithm remains the computed tomography scan (CT) given its speed of use and sensitivity. CT-angiography (CTA) is crucial in diagnosing large-vessel occlusions (LVOs) and multiphase CTA and CT-perfusion (CTP) can demonstrate the number of collaterals in the area and remaining salvageable tissue. MRI can be used to select patients presenting in an unknown time window for thrombolysis. The primary goal of AIS management is to rescue the ischemic penumbra and the approach to treating AIS has gone from a time-based to tissue-based approach. While tPA is still the agent of choice for thrombolysis in patients with AIS, tenecteplase (TNK) may be just as effective and more efficient to use. Endovascular thrombectomy (EVT) has shown considerable efficacy for alleviating LVOs and using CTP, patients can be selected for hours after symptom-onset if viable tissue remains. It remains unclear if an “EVT-alone” strategy is superior to “tPA + EVT” strategy but this may be dependent on clot, patient, and geographical characteristics.

Keywords: stroke, ischemia, neuroimaging, thrombolysis, thrombectomy

1. Introduction

Globally, stroke remains the second leading cause of death and the third leading cause of death and disability (as expressed by disability-adjusted life-years lost—DALYs) [1]. 88% of all acute strokes are ischemic strokes, caused by reduced blood flow and of the remaining, 10% are intracerebral hemorrhages, due to rupture of cerebral arteries and 2% subarachnoid hemorrhages, due to trauma or rupture of aneurysm [2]. This chapter will focus on acute ischemic strokes (AIS). Among AIS, 22% are cardioembolic (thrombus originally formed in the heart), 23% due to large artery atherosclerosis, 22% due to small vessel occlusion or lacunar infarct (2–20 mm in size and occur deep in the brain), and 29% are other causes [3, 4].

The typical presentation of AIS is abrupt focal neurological deficit that is due to a lack of blood flow [5, 6]. As neurological dysfunctions caused by focal brain, retinal or spinal cord ischemia may be reversible if presented early and treated promptly, acute stroke care at the hospital setting should begin with prompt history taking, neurological exam, emergent neuroimaging and pertinent investigations to establish a plan of management [7].
The TOAST (Trial of Org 10,172 in Acute Stroke Treatment), classification categorizes ischemic stroke etiologies into five major subtypes [8]: large artery sclerosis, cardioembolism, small artery occlusion, stroke of other determined cause, and stroke of undetermined cause. Newer classification criteria such as the Causative Classification System further stratifies high and low risk cardiac sources of embolism. In this system, the 'stroke of undetermined cause' category is divided into unknown, incomplete evaluation, unclassified stroke with more than one etiology, and cryptogenic embolism, where there is evidence of embolism in otherwise normal looking artery or subsequent complete recanalization [9].

Other disorders may masquerade as ischemic strokes (Table 1). Between 15 and 25% stroke suspects presented to the emergency room are stroke mimics [2, 5]. Patients who have seizures often present with post-ictal hemiparesis, also known as Todd’s Paresis. This is a transient weakness that usually resolves within 24 hours [10]. Migraine auras may present as motor weakness, aphasia, sensory disturbances, and visual auras, that potentially resemble stroke symptoms. Focal neurological deficits are frequently the sequelae of severe hypoglycemia, necessitating blood glucose measurements. Tumors can cause seizures, may directly compress surrounding vessels, and can be easily ruled out with MR brain. Other stroke mimics include hyponatremia, conversion disorder, and positional vertigo [11]. The key to ruling out the mimics is through heightened clinical suspicion and tailored investigations.

2. Diagnosis of acute ischemic stroke

2.1 Last known normal time (LKNT)

The ECASS III trial has established that thrombolysis efficacy was significant up to 4.5 hours post stroke [12]. The precise onset of stroke allows a clear decision on whether to provide thrombolysis. However, 1 in 7 strokes are a wake-up stroke, and oftentimes patients and their families were vague about the time onset [13]. A key piece of information in the history of present illnesses is the LKN, which establishes the maximal duration from onset to presentation for those without a precisely known onset.

| Seizures |
| Migraine with aura |
| Infection: encephalitis, brain abscess |
| Metabolic: Hypo/hyperglycemia, hyponatremia, Wernicke's encephalopathy |
| Neoplasia: CNS tumor, CNS metastasis |
| Drug toxicity |
| Hypertensive encephalopathy |
| Positional vertigo |
| Conversion disorder |

Table 1. Differential diagnosis to stroke.
2.2 Rapid acquisition of medical and surgical history

Pertinent history and neurological exam are essential to establish a stroke diagnosis and guide subsequent treatment. History not only provide clues for potential stroke etiologies, but also detects contraindications for thrombolysis (discussed in detail later) and guide stroke prevention. Of particular importance in medical history are vascular risk factors, including modifiable conditions such as obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, chronic obstructive pulmonary disease, previous ischemic or hemorrhagic strokes, ischemic heart disease, congestive heart failure, atrial fibrillation, smoking, and excessive alcohol use [14]. The presence of some or many of these factors increase the likelihood of AIS.

2.3 Focused neurological exam and use of NIHSS score

After history is obtained, the clinician should perform a focused neurological exam, calculating National Institutes of Health Stroke Scale (NIHSS) score, originally used for the NINDS Trial [15]. The NIHSS is a standardized scale ranging from 0 to 42 that grades patient’s level of consciousness, language, visual fields, facial weakness, limb weakness, sensation, and incoordination [16]. Each category has a different score and a higher score for a component would indicate a worse deficit (for example, when testing left arm weakness, a score of 0 would mean no weakness, and 4 would indicate flaccid paralysis of the arm).

The NIHSS score strongly correlates with post-stroke modified Rankin scale (mRS) score\(^1\) at discharge from stroke stay [17, 18]. An NIHSS <5 is predictive of better outcomes with an mRS generally less than 3, and an NIHSS >22 predictive for poorer outcomes with an mRS greater than 3 or death. NIHSS scores between 5 and 22 inclusive on the other hand had a weaker correlation with mRS scores [19]. However, on the NIHSS, left hemispheric deficits are more heavily rated than those of the right [20]. Further the scores do not reliably detect posterior circulation findings, for example, vertigo and dizziness [21]. Nevertheless, the NIHSS is known as a reliable predictor for stroke severity, informing treatment decisions and post-thrombolysis prognosis. Of note, neurological exams should not be entirely limited to the items of the NIHSS, as the signs outside of those of NIHSS may inform alternate explanations. For example, a new vertical gaze palsy points to a midbrain localization and an acute onset dysphagia with saliva pooling may be caused by posterior circulation infarct. These are examples of signs separate from the NIHSS, and a rapid and focused neurological exam should not miss.

2.4 Emergent acquisition and interpretation of brain imaging

2.4.1 Non-contrast computed tomography (NCCT) brain

Ideally, within 25 minutes after presenting at the hospital, a non-contrast CT (NCCT) brain with an axial section thickness no more than 5 mm may detect the

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\(^1\) The MRS is a scale that measures disability from stroke that is scored from 0 to 5 with a higher score indicating higher disability. A score of 0 means no disability, 1 means mild symptoms, 2 means inability to carry out previous activities, 3 means requiring help but able to walk, 4 means inability to walk without assistance, and 5 means, bedridden.
following: acute hemorrhage which is an absolute contraindication to IV tPA, early ischemic changes, chronic infarcts, and dense artery sign [7, 22]. NCCT has a sensitivity and specificity exceeding 95–98% for the detection of intracranial hemorrhage [23]. Hypoattenuation (dark on NCCT) of gray matter, in forms of the insular ribbon sign defined by loss of gray-white distinction, obscured outline and partial disappearance of the lentiform nucleus, and loss of gray-white matter differentiation, tend to be subtle when patients present early [24, 25]. The hyperdense artery sign (Figure 1) can be seen within 90 minutes of an MCA stroke and is usually caused by thromboembolic material in the lumen of the MCA [24] but can also commonly seen in the anterior cerebral artery (ACA), posterior cerebral artery (PCA), and basilar artery [26].

2.4.2 The Alberta stroke program early CT score (ASPECTS), a treatment and prognosis tool

NCCT allows computing the ASPECTS, which assesses early ischemic changes in the anterior circulation using 10 anatomically defined regions: 1 point for subcortical structures such as the caudate, lentiform, internal capsule, insular ribbon, and 6 for cortical MCA territories designated M1 to M6 [27, 28]. Therefore, an ASPECTS of 10 indicates no ischemic change in the above territories but does not eliminate infarcts in posterior circulation territories, and an ASPECTS of 0 is tantamount to very large infarcts that involves all the above anterior circulation territories. ASPECTS has a sensitivity of 78% and specificity of 96% for predicting functional outcome [27]. As the score predicts functional independence after thrombolysis, one generally requires a cut off score of 6 or more, age older than 18, an NIHSS score of 6 or more, and a

Figure 1. Non-contrast CT scan demonstrating hyperdense left middle cerebral artery sign (arrow). It is evident that the vessel shows up as brighter or hyperdense, compared to the contralateral vessel. A clot in the artery is more dense as it contains more red blood cells and therefore, more iron.
reasonable pre-stroke functional baseline to be eligible for thrombectomy, as will be discussed later [29]. There are however drawbacks to the ASPECTS. First, it is not helpful for strokes in the posterior circulation. Second, there is significant variation in interrater reliability. Finally, ASPECTS can be affected by the quality of the NCCT as well as bone and metal artifacts [24].

2.4.3 CT angiography

CT angiography (CTA) requires administering iodinated contrast material through an 18–20 gauge needle, and it is not necessary to obtain the results of renal function prior to CTA [30]. Ehrlich et al. studied safety of CTA in evaluation of patients with acute stroke [31]. Within 24 to 48 hours after CTA, they found no statistical difference in both renal function and changes in creatinine. They drew the conclusion that CTA should not be delayed for testing for creatinine in AIS. CTA is performed immediately after the NCCT, with the aim to visualize occlusions in both extracranial and intracranial vasculature from the aortic arch to vertex [24] and may be performed as a single, delayed, or multiphase study (Figure 2). Evidence suggests that performing CTA is all individuals presenting within 24 hours improved detection of LVO, increased the population of AIS patients treated with endovascular thrombectomy, and was associated with better outcome [32].

Thus, CTA may reliably discover locations of stenosis and occlusions, providing clues to etiologies and allowing further assessments for the eligibility of thrombectomy. As an example, an occlusion in the internal carotid (ICA) with ipsilateral infarct may sway the etiology towards thromboembolism originated from a large vessel, while stenosis of the ICA with bilateral embolic showers is more commonly caused by an embolism from a proximal source such as the heart of aortic arch.

Figure 2.
CT angiogram with circle of Willis reconstruction. After the region marked by the red arrow, there is no contrast filling the artery indicating an occlusion in the distal M1 branch of the left middle cerebral artery.
Multiphase CTA (mCTA) is an imaging tool that provides three time-resolved images of pial arterial filling in the whole brain and is superior to conventional single-phase CT angiography (sCTA) [33]. After injection of contrast bolus, the first phase, also known as the peak arterial phase, scans from the aortic arch through the vertex. The second phase, the peak venous phase, scans the skull base through the vertex, and is performed 4 seconds after completion of the peak arterial phase scan. The third phase, the late venous phase, scans from the skull base through the vertex performed 4 seconds after completion of the second phase. Multiphase CTA (mCTA) is especially useful in assessing collateral vasculature. Collaterals are connections between cerebral blood vessels; when an artery is occluded, these collaterals reroute blood flow to maintain perfusion to the ischemic tissue [24]. Patients with diminished or absent collateral vessels in the symptomatic hemisphere experienced markedly higher risk for further deterioration. Compared to sCTA, mCTA improves detection of large-vessel occlusion (LVO; occlusion of large artery in brain such as terminus of the ICA, M1/M2 branch of MCA, ACA, and basilar artery), improved characterization of collateral status, improved tolerance of patient motion and poor hemodynamics, and higher interrater reliability [34]. Therefore, the mCTA is incredibly useful in determining prognosis and guiding treatment decisions [24, 35, 36].

2.4.4 The concept of the ischemic penumbra and mismatch

In a patient presenting with AIS, there exists an ischemic “penumbra” [37]. This is the region which receives greater than 10% of its baseline blood flow but less than 30% [38]. This tissue has not irreversibly infarcted yet, but the neurons are electrically silent (i.e. not conducting action potentials) and causing the patient’s acute clinical deficits. The tissue that is already infarcted and cannot be recovered, even after reperfusion is called the ischemic “core”. Figure 3 depicts a rat model of the effect of decreased blood flow on neuronal physiology. In humans, estimates of the ischemic penumbra have been best achieved using CT-perfusion (CTP) and MRI. Using imaging modalities, we can determine which tissue is being hypoperfused, the volume of tissue being hypoperfused, and the volume of tissue that is already infarcted. The ratio between the total volume of tissue being hypoperfused and the volume of tissue that is already infarcted, the core, is known as the mismatch ratio (MMR). To define the specifics of the MMR, it is important to discuss CTP parameters.

2.4.4.1 The parameters of CTP

CTP is the accepted modality for selecting patients with AIS within 6 to 24 hours of LKNT, as it is can determine how much salvageable tissue remains [24]. There are four primary parameters that CTP uses to determine if tissue is hypoperfused and if so, if can be saved. Cerebral blood flow (CBF) is the volume of blood flowing in a unit (100 g) of brain tissue during a unit of time (1 minute). Time-to-maximum (Tmax) is the time delay between the contrast arriving in the large vessels to when it arrives in brain tissue. Cerebral blood volume (CBV) is the volume of blood/contrast in mL per 100 g of brain tissue. Finally, mean-transit-time (MTT) is the average time required for the blood/contrast to traverse the 100 g of brain tissue. Automated software computes these qualitative and quantitative maps of ischemic lesion tissue [39]. Table 2 presents a visual comparison of CTP parameters distinguishing core from penumbra.
A rat model of the effect of decreased cerebral blood flow (CBF; measured in mL/100 g/min) on neuronal physiology and brain tissue. Below 15 mL/100 g/min, ATP is depleted, Na/K pumps fail, and cells die, forming the ischemic core. Below 35 mL/100 g/min, there is a change in neuronal metabolism and the neuron is not conducting action potentials. The tissue is non-functional but has not infarcted yet. This is the ischemic penumbra, the region that is still salvageable by intervention and "doomed to die" without it. Below 55 mL/100 g/min, the tissue is "at risk" but will not necessarily die, even without intervention. Adapted from lieu et al. 2020.

<table>
<thead>
<tr>
<th>Measurement parameter</th>
<th>Core</th>
<th>Penumbra</th>
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<tbody>
<tr>
<td>Mean Transit Time (MTT)</td>
<td></td>
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<td>T Max</td>
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<tr>
<td>Cerebral Blood Flow (CBF)</td>
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<tr>
<td>Cerebral Blood Volume (CBV)</td>
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Table 2. CT perfusion measurements for core and penumbra. In both the core and the penumbra, due to blockage of the artery, there is less flow of blood to the tissue, leading to decreased CBF. The blood is also taking longer to fill and to leave the tissue and therefore, MTT and T max are increased. In the core infarct, cerebral blood volume is decreased as blood is no longer filling the dead tissue.
The penumbra can be determined by subtracting the ischemic core from the tissue at risk. There have been multiple methods of estimating the tissue-at-risk or the perfusion deficit as well as estimating the ischemic core. Visually, comparing MTT maps to CBV maps gives a qualitative estimate of the penumbra (Figure 4). The most useful quantitative measurements are Tmax > 6 s, which best estimates tissue-at-risk and CBF < 30 ml/100 g/min, which best estimates core [40]. One can also calculate the MMR, which is the ratio between the core volume and perfusion deficit volume. These numbers are crucial as they determine eligibility for endovascular thrombectomy. To be eligible for the intervention, the MMR must be greater than 1.8, the penumbra must be greater than 15 mL, and the Tmax > 10 seconds [41].

There are caveats pertaining to potential inaccuracy of the above parameters. CTP parameters may be affected by reduced cardiac output, carotid artery stenosis, and injection rate. Technical factors such as motion artifacts, and erroneous CTP protocol, for example wrong contrast injection rate, can also bias the computation of ischemic core and penumbra [39]. A perfusion protocol shorter than 60 seconds, as a further example, is known to overestimate the infarct core volume [30]. Occasionally CTP results can be entirely misleading when a non-stroke hemisphere is labeled as ischemic due to recanalization and luxury hyperperfusion of the stroked hemisphere [42]. Stroke mimics causing vascular dysregulation, such as seizures, hypertensive encephalopathy, hemiplegic migraines, may produce false images of penumbra, and so can vascular anatomical variations [39]. Although CTP has become standard in assessing anterior circulation stroke, there is to date insufficient evidence for its application in posterior circulation strokes. In particular, the CBF cut off of 30%, a defining feature of the ischemic core, can only be applied to anterior circulation strokes. MRI on the other hand is considered the gold standard for assessing posterior circulation infarcts [43].

Figure 4.
CT perfusion map of a patient with acute left MCA occlusion with mean transit time map (MTT; left) and cerebral blood volume map (CBV; right) demonstrating acute occlusion of left MCA. In the MTT map, increased time is indicated by a color higher on the spectrum with the longest time being red. It can be seen that the region marked by the white arrow has a prolonged MTT versus the right hemisphere. On the CBV map, the color lower on the spectrum demonstrates lower CBV.
2.4.4.2 Magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI)- fluid attenuated inversion recovery (FLAIR) mismatch

Another method of determining mismatch is by using magnetic resonance imaging (MRI). This is a newer, more sensitive form of imaging compared to CT. Its primary advantages are its high spatial resolution and versatility in use. Its main disadvantages are that the images take longer than CT to acquire and the scanners are not nearly as common or accessible as for CT. Nevertheless, specific MRI sequences can provide crucial information for the diagnosis of AIS. A diffusion-weighted imaging (DWI) measures the diffusion of water molecules across the cellular membrane [44]. In patients with AIS, due to disruption of the electrochemical gradient, this diffusion is disrupted. This shows up at hyperintense or bright on imaging. This bright signal can be detected for at least 2 weeks after the initial event [45]. The apparent diffusion coefficient (ADC) image is the inverse of the DWI and has low intensity during this period. The DWI and ADC image are useful in demonstrating whether there is any ischemia to a region, reversible or irreversible. The T2 fluid attenuated inversion recovery (FLAIR) image is the sequence that is used to see the structure and anatomy of the brain tissue. In the hyperacute phase, the FLAIR has variable intensity and increases in intensity after 6 hours. The FLAIR image demonstrates structural damage and irreversible infarcted tissue [44]. To be a candidate for endovascular thrombectomy, the DWI volume must be greater than 70 mL [40]. In situations of uncertain onset, positive DWI with negative FLAIR, known as a DWI-FLAIR mismatch, strongly suggest that the stroke is hyperacute and there is significant mismatch (Figure 4). Using DWI-FLAIR mismatch, once can predict if an AIS is presenting within 4.5 h of LKNT with 62% (95% CI: 57–67) sensitivity, 78% (95% CI: 72–84) specificity, 83% (95% CI: 79–88) positive predictive value, and 54% (95% CI: 48–60) negative predictive value [46]. Therefore, in patients in whom LKNT is unknown, MRI DWI-FLAIR mismatch can be used to identify patients who would still remain candidates for thrombolysis, which will be discussed in detail later [47].

There are a plethora of other MR sequences and techniques that can be used in the diagnosis and management of AIS. Susceptibility weighted imaging (SWI) is a sequence that is sensitive to products that especially distort the magnetic field like iron. Given blood breakdown products contain iron, SWI provides information about the existence of possible hemorrhagic transformation has occurred within the first 12 hours [25, 48]. MR angiography without contrast (time-of-flight) is an alternative to CT angiography [49]. And MR perfusion has obtained 90% concordance between CT-based and MR-based mismatch status [40], and is a highly reliable alternative for patients not amenable to NCCT and CTA.

2.5 Emergent bloodwork

Emergent laboratory investigations should include complete blood count, electrolytes, aPTT, INR, creatinine, and glucose [7]. It is not necessary to wait for all the results before thrombolysis, as blood glucose can be reliably given by a finger stick test, and as mentioned, creatinine values are not needed prior to performing CTA. Other labs such as an INR > 1.7, platelets <100,000/mm³, and blood glucose <50 mg/dL, are also helpful as they are part of the relative contraindications for tPA, discussed in further detail later. Patients suspected of having ischemic strokes should have a 12-lead EKG and initiate telemetry. This may assess cardiac rhythm and uncover atrial fibrillation [50].
3. Treatment of acute ischemic stroke

3.1 Introduction

As discussed in the previous section, the prompt recognition of AIS using physical exam and its diagnosis using non-contrast CT (NCCT), CT-angiography (CTA), and CT Perfusion (CTP) is the first step in the efficient and effective management. In the last two decades, we have learned much about the treatment of AIS beginning with the concept of the “ischemic penumbra” to the use of thrombolysis in AIS and finally, to the revolutionary procedure of mechanical thrombectomy.

3.2 Principles of treatment

As mentioned previously, there exists an ischemic penumbra in patients with AIS, tissue that is at risk but that has not yet infarcted. The primary goal of AIS management is to use interventions to recanalize the occluded artery and restore perfusion to the penumbra [38]. These interventions and these patients must be selected carefully to maximize benefit and avoid harm. In the following section, these interventions and the selection process will be discussed.

3.3 Thrombolysis

One of the methods of recanalizing the occluded artery is by breaking up the thrombus using intravenous pharmacotherapy. Thrombi that occlude intracerebral arteries are created when the protein fibrin creates strands of protein that are long and insoluble [51]. The insoluble protein binds to platelets and the cross-linked fibrin forms a mesh over the platelet-protein complex forming a plug. Thrombolytic/fibrinolytic drugs such as alteplase, or tissue-plasminogen activator (tPA) cleave the inactive protein plasminogen into its active form plasmin. Plasmin degrades the fibrin matrix that was reinforcing the thrombus, thereby allowing clot breakdown and recanalization. In 1995, the landmark NINDS trial [15] demonstrated that patients with AIS that received tPA within 3 hours of patient LKNT had a significantly higher likelihood of favorable outcome (39%) at 3 month follow-up compared to those who received placebo (26%) as measured by the Modified Rankin Scale (Odds ratio: 1.7). However, there was also a significantly higher risk of symptomatic intracerebral hemorrhage (ICH; Table 3) in the tPA group (6.4%) versus the placebo group (0.6%). It was not until 2008 “European Cooperative Acute Stroke Study” (ECASS) III trial [52], that the tPA window was extended to 4.5 hours. A subsequent systematic review of four clinical trials investigating thrombolysis [55] determined that, as the time to symptom onset increases, the benefit from tPA declines and the risk of mortality increases. Beyond the 4.5 hour window, the risk of tPA outweighs the benefits (Figure 4). In a metaanalysis of 6756 patients from nine studies [56], the authors found that patients who received tPA and a 5.55% increase in absolute risk of parenchymal type II hematoma [54] (Odds ratio: 5.55), 3.1% increase in absolute risk of SITS-MOST ICH (Odds ratio: 6.67), and 2.3% increase in absolute risk of fatal ICH (Odds ratio: 7.14). One of the main caveats of thrombolysis is that the clinician must know the patient’s LKNT. There are a significant proportion of patients that in whom the time of symptom onset is unknown. Traditionally, these patients would not be candidates for thrombolysis as the benefit-to-risk ratio would not be known. However, the landmark WAKE-UP trial, investigated the use of thrombolysis in this
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DOI: http://dx.doi.org/10.5772/intechopen.106389

The authors used MRI with diffusion to determine if there was still a significant volume of penumbra and mismatch, and in carefully selected patients, thrombolysis was administered. There was a greater likelihood of favorable outcome in patients administered tPA (53.3%) versus those who received placebo (41.8%) at 3 months (Odds ratio: 1.61). In the DIAS trial, the authors used a highly fibrin-specific thrombolytic agent, desmoteplase, in patients presenting with AIS [57]. The patients presented between 3 and 9 hours from LKNT and were carefully selected by use of MRI to determine who would be a good candidate for thrombolysis. A higher rate of reperfusion and favorable outcome was seen in patients who were given thrombolysis (71.4% and 60.0%) compared with those who received placebo (19.2% and 22.2%). Therefore, if a center does have MRI capabilities, carefully selected patients with AIS with unknown time of symptom onset may be candidates for thrombolysis.

Table 4 shows the indications and contraindications for thrombolysis for patients presenting with AIS [7]. The only absolute contraindication to administration of thrombolysis is demonstration of ICH on NCCT. The other criteria listed are relative and are dependent on the clinical situation. For a patient to be a candidate for thrombolysis, the stroke should be classified as clinically disabling, usually referring to a NIHSS>5. While NIHSS >5 is usually used as the standard for clinically disabling, there are exceptions to this. For example, a patient presenting with AIHS who demonstrates global aphasia would have a NIHSS of 4. However, this would be significantly disabling for the patient and therefore, he would likely qualify for thrombolysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of symptomatic ICH</th>
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<tr>
<td>NINDS</td>
<td>Any new ICH on NCCT associated with any neurologic deterioration [15]</td>
</tr>
<tr>
<td>ECASS III</td>
<td>If associated with neurological decline of an increase of ≥4 points on the NIHSS [52]</td>
</tr>
<tr>
<td>SITS-MOST</td>
<td>Parenchymal hematoma type 2 on imaging 22–36 hours after intervention with neurological deterioration of ≥4 points on NIHSS [53]</td>
</tr>
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*A hematoma which occupies 30% or more of the infarcted tissue and is accompanied with obvious mass effect on adjacent tissue [54].*

Table 3.
Different definitions of symptomatic ICH depending on clinical trial [47]. The NINDS trial used the most liberal definition, explaining the higher estimates of ICH compared to what was reported in subsequent studies.

Once it is determined that a patient is a candidate for thrombolysis, the dosing should be calculated, and formulation prepared. The dose that is primarily used for AIS is 0.9 mg/kg of patient’s ideal body weight, with a maximum dose of 90 mg [7]. Of the total dose, 10% is administered as a bolus over 1 minute and the remainder as an infusion over 60 minutes. The ENCHANTED trial investigated a lower dose of tPA, 0.6 mg/kg in a cohort of Asian patients presenting with AIS and although they demonstrated a lower risk of ICH compared to standard dose (1% vs. 2.1%), the trial was not able to show noninferiority of the lower dose with respect to death or disability at 3 months [59]. While alteplase is standard of care for thrombolysis in AIS, in the last 10 years, there is evidence suggesting that tenecteplase (TNK) the
medication used in thrombolysis for acute myocardial infarctions, is as safe and at least as effective as tPA [60–62]. The primary advantages to TNK would be its longer half-life, eliminating the need for a 60 minute infusion, and its greater specificity for fibrin, which could mean more effective thrombolysis [2]. There are currently large-scale clinical trials underway to determine the non-inferiority of TNK compared to tPA (NOR-TEST) and efficacy and safety of TNK in patients presenting more than 4.5 hours since LKNT (TIMELESS), and in patients with basilar artery occlusions (POST-ETERNAL). In the next 10 years, TNK may indeed be the standard of practice.

There are two primary complications that can occur from thrombolysis administration in the acute phase. The first is angioedema and this might occur minutes to hours after administration of tPA [51]. As mentioned earlier, tPA cleaves plasminogen into its active form plasmin. Plasmin activates complement as well as the kinin pathways which leads to an inflammatory response and an increase in systemic cytokines. Therefore, it should not be surprising that one of the consequences of tPA administration is angioedema, an acute albeit transient swelling of deeper layers of the skin and mucosa. The swelling is red and well-circumscribed and usually involves the orolingual, periorbital, and pharyngeal regions. Angioedema is seen in approximately 5% of patients who receive tPA and is usually mild and patients who are on ACE inhibitors are at higher risk [63]. These patients require careful monitoring as if the swelling becomes severe and involves the airway, the patient may need intubation. Usually the angioedema is mild and self-resolves after the tPA infusion is complete. The signs and symptoms of the reaction can be managed by IV diphenhydramine and/or ranitidine histamine (H1) receptor antagonists [64].

The second major complication of tPA administration, which was alluded to earlier, is ICH. ICH can occur in up to 7% of tPA administrations and can be associated with up to 83% mortality [65]. Patients must be counseled about this increased risk to make an informed decision about receiving tPA and clinicians should be aware of the risk of ICH to recognize and manage it promptly. The factors associated with a higher risk of ICH include larger volume of hypoperfused tissue, larger established infarct, higher NIHSS, and higher glucose and/or blood pressure at the time of tPA

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
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<td>Clinically disabling AIS (NIHSS&gt;5) with known time of onset ≤4.5 hours</td>
<td>Intracerebral Hemorrhage on CT</td>
</tr>
<tr>
<td>BP &lt;185/110 mmHg</td>
<td>Anticoagulation (thrombin or factor Xa inhibitors)</td>
</tr>
<tr>
<td>Blood glucose &gt;50 mg/dL</td>
<td>History of intracranial hemorrhage</td>
</tr>
</tbody>
</table>

Table 4. Indications and contraindications for tPA [7]. Importantly, the only absolute contraindication to tPA use is intracerebral hemorrhage on noncontrast CT. The rest are dependent on the clinical scenario.
administration [64, 66]. Therefore, patients who receive tPA must have their systolic blood pressure kept below 185mmHg and be euglycemic. In all patients who receive tPA, a NCCT should be repeated 24 hours post-administration. Even if a patient does not have a hemorrhage large enough to cause clinical deficits or change in level of consciousness, the size and location of the ICH will influence future decisions about secondary stroke prevention. The clinician should have a low threshold to order a stat repeat NCCT earlier than 24 hours if there is a clinical deterioration of the patient.

In summary, tPA is an effective tool in the management of AIS in carefully selected patients in whom the benefits of thrombolysis outweigh the risk of hemorrhage. Unfortunately, a significant number of patients present with AIS outside of the 4.5 hour window or meeting another contraindication to tPA. In 2015, a new hope of treatment emerged for these patients.

3.4 Endovascular thrombectomy

While thrombolysis is effective for a select group of patients, it is accompanied by several limitations. First, given that this is a systemic fibrinolytic medication, it is accompanied with the risk of bleeding anywhere in the body, especially in the brain. Second, only select patients qualify for its administration. Third, the rate of recanalization for proximal, large-vessel occlusions (LVOs) is poor, ranging from 13–50% [2, 67]. These are dense clots that are in the major arteries in the brain (the terminus of the internal carotid artery, the early branches of middle cerebral artery (MCA; M1, M2), and the basilar artery), even though these occlusions make up at least one-third of strokes [67] and can cause significant disability.

These three disadvantages are not shared by the endovascular thrombectomy (EVT) procedure. In this procedure, a patient is taken to interventional neuroradiology suite, IV contrast is administered to the patient which sequential x-rays of the head and neck are obtained. An occlusion is localized when it is evident that there an abrupt

Figure 5.
MRI of patient with acute right middle cerebral artery stroke with DWI on the left and FLAIR on the right. In the DWI image, the white circle marks an area of diffusion restriction indicating acute ischemia. However, there are minimal to no changes in the corresponding FLAIR image. This indicates that a significant core has not yet formed yet and mismatch exists.
halt of contrast filling the artery. A catheter attached to a wire is inserted into the femoral artery and advanced until it reaches the clot, which can then be aspirated or retrieved using a stent (Figure 5). The first trials to examine the benefit of EVT were performed in 2013 and did not show the procedure to be clinically efficacious [2]. This changed with the advent of new methods of imaging and better catheters and in 2015, the “Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands” (MR CLEAN) trial demonstrated that patients that received EVT within 6 hours of symptom onset were more likely to achieve functional independence at 3 months (32.6%) compared to those who received placebo (19.1%) [68]. Other trials confirmed the findings of MR CLEAN and thus emerged new guidelines for the eligibility for EVT: 1) patients ≥ 18 who presented 2) within 6 hours of symptom onset with a 3) LVO, a 4) NIHSS ≥ 6 and an 5) ASPECTS score of CT ≥ 6 on NCCT [7]. With the introduction of CTP, clinicians could identify core and penumbra in patients with AIS and determine which patients could still benefit from intervention. In the subsequent AURORA, DEFUSE 3 and DAWN trials, it was determined that EVT could be safe and effective in patients presenting up to 24 hours post symptom onset [69–71]. However, if a patient presents outside of the initial six-hour window, they must receive a CT perfusion or MRI with DWI to determine the volume of core infarct that exists and if there is still mismatch; otherwise it will be impossible to determine if the patient could benefit from the procedure. As mentioned earlier, there are specific CTP criteria that allow a patient to be eligible for EVT if they present outside of the initial 6 hour window. The MMR must be greater than 1.8, the penumbra must be greater than 15 mL, and the Tmax >10 seconds [41]. The HERMES meta-analysis of five EVT trials found that patients who received standard of care without EVT had a 14% higher absolute risk of not having a favorable outcome compared to those who received EVT. There was no significant difference in symptomatic hemorrhage between groups. Therefore, it is now standard of care to consider each patient who presents within 24 hours with a proximal LVO for EVT [72]. Unfortunately, not all AIS patients are eligible for EVT. The patient must have a proximal LVO to be accessible by the current clot-retrieval tools. As clots become more distal, there is a lower likelihood of successful procedure and higher likelihood of complications. While experienced interventionalists may go after clots in the basilar artery, anterior cerebral arteries, and distal middle cerebral arteries, there is little evidence to suggest the efficacy of these procedures. Second, not all AIS patients have access to EVT. The intervention is only offered at major, tertiary care centers. While thrombolysis can be done even in remote settings with neurologists guiding the treatment via “telestroke”, for EVT a patient needs to be transferred, often over hundreds of kilometers, to obtain the procedure and by the time they reach the EVT site, there may be no penumbra left [2].

EVT is also accompanied by its own risks [73]. While ICH is more common with tPA, there is still a risk of hemorrhagic transformation with EVT as causing reperfusion to already infarcted tissue can cause injury, edema, and resulting hemorrhage. As this is an interventional procedure, there is always the risk of infection or clot developing at the site of entry. When the interventionalist is trying to access the occlusion, pieces of the clot can break off and move distally creating occlusions not accessible by the catheter. In rare cases, arteries can be damaged or even ruptured from the catheter itself.

Despite the disadvantages to EVT, it remains at the forefront of AIS therapy. The advent of EVT has revolutionized stroke protocols and care across the world with the acute stroke window being extended from a mere 4.5 to an entire day.
Given the advantages of EVT, the question arises of whether patients with LVO should go straight for EVT or if they would benefit from tPA administration first. There have been multiple trials that have compared the use of EVT alone to EVT combined with thrombolysis and have yielded mixed results. The “Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands-NO IV” (MR-CLEAN-NO IV) [74] and “Randomized study of endovascular therapy with versus without intravenous tissue plasminogen activator in acute stroke with ICA and M1 occlusion” (SKIP) trials [75] did not demonstrate noninferiority of EVT alone compared to EVT and tPA whereas the DIRECT MT [76] and DEVT trials [77] demonstrated that EVT alone was indeed noninferior. The different results of the studies may have been due to different characteristics of the study population or of the study design itself. For example, in the DEVT trial, the population had a higher proportion of patients with intracranial atherosclerosis which can change the benefit obtained with thrombolysis. There is currently not enough evidence to suggest a strategy of EVT alone for patients presenting with AIS who have LVOs. It is necessary to determine if there is a particular subgroup that would benefit from EVT alone and tPA whereas the DIRECT MT [76] and DEVT trials [77] demonstrated that EVT alone was indeed noninferior. The different results of the studies may have been due to different characteristics of the study population or of the study design itself. For example, in the DEVT trial, the population had a higher proportion of patients with intracranial atherosclerosis which can change the benefit obtained with thrombolysis. There is currently not enough evidence to suggest a strategy of EVT alone for patients presenting with AIS who have LVOs. It is necessary to determine if there is a particular subgroup that would benefit from EVT alone [78]. For example, according to DIRECT MT and MR-CLEAN-NOIV, patients with tandem occlusions (simultaneous blockage of both internal carotid artery and middle cerebral artery) may benefit from EVT alone. Patients with large ischemic cores who receive EVT alone may also have decreased likelihood of symptomatic ICH as per all of the trials except MR-CLEAN-NOIV. At the same time, taking the time to select these patient subgroups in a clinical scenario may be detrimental to those who would benefit from both EVT and tPA. Table 5 illustrates the specific factors that could favor an EVT alone strategy as well as factors that would favor a thrombolysis and EVT strategy [79]. As per current guidelines, patients presenting with LVO not meeting the contraindications to thrombolysis should receive thrombolysis as long as it does not delay the patient receiving EVT (Figures 6 and 7) [7].

### Table 5

<table>
<thead>
<tr>
<th>Reperfusion advantages</th>
<th>Complications with tPA</th>
<th>Geographic factors</th>
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</thead>
<tbody>
<tr>
<td>Longer clots</td>
<td>Full basal ganglia infarction</td>
<td>Fast local workflow</td>
</tr>
<tr>
<td>Tandem Occlusions</td>
<td>Severe hyperglycemia</td>
<td>High costs of tPA</td>
</tr>
<tr>
<td>Longer times from LKNT</td>
<td>Higher age of patient</td>
<td>Thrombectomy team available</td>
</tr>
<tr>
<td>Proximal Occlusions</td>
<td>Severe microangiopathy</td>
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<table>
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<tr>
<th>Reperfusion advantages</th>
<th>Delays with EVT</th>
<th>Geographic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter clots</td>
<td>Unfavorable vascular anatomy</td>
<td>Prolonged local workflow</td>
</tr>
<tr>
<td>Good Collaterals</td>
<td>Delays with anesthesia</td>
<td>Low costs of tPA</td>
</tr>
<tr>
<td>Earlier presentation</td>
<td>EVT team not readily available</td>
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</tbody>
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Adapted from Nogueira et al. [79].

3.5 Post-acute care

In the acute window, in patients who receive intervention or have a very large infarct, it is essential to monitor heart rate and blood pressure every 15 minutes for
2 hours, every 30 minutes for 6 hours, and every 60 minutes until 24 hours after starting treatment [80]. It is also pertinent to monitor the patients’ neurovitals, their level of consciousness, strength, and language to ensure their clinical status is not deteriorating. As previously discussed, there should be a low threshold for repeating a NCCT in the acute period. Patients with AIS should also be kept NPO until their swallowing is assessed formally as their decreased level of consciousness and facial weakness can increase the likelihood of aspiration. All stroke patients who receive tPA, EVT, or who present with significant deficits, should be admitted to a dedicated stroke unit where
they can be monitored closely by stroke specialists and an interdisciplinary team of nurses, physiotherapists, speech and language pathologists, and dieticians to ensure favorable functional outcome. Evidence suggests that patients that are cared for at an acute stroke unit have less likelihood of disability and mortality compared to those that are admitted to a general ward [81]. Early rehabilitation is crucial in preventing long-term disability and early management of blood pressure, diabetes, cholesterol, and antiplatelet/anticoagulant therapy is crucial in the secondary prevention of stroke.

4. Conclusion

Gone are the days in which AIS was thought to be a terminal disease. Since The National Institutes of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS) trial in 1995 there have been numerous advances which have prevented patients from long-term disability. Both thrombolysis and EVT are potential treatments for carefully selected patients presenting with AIS and each has its benefits as well as disadvantages. However, there still exist a major proportion of the stroke population that does not qualify for either therapy, either because they have presented out of the window or because there is no LVO. There are numerous trials underway and show promise to cover a wider population. For example, the trial TEMPO II is examining the use of thrombolysis in patients presenting with minor stroke, NIHSS<6. The TIMELESS trial is investigating the use of thrombolysis in patients presenting outside of the 4.5 hour window who would still be a candidate for EVT. Finally, better catheters and stent-retrievers are being developed to reach more distal clots without increasing complications. There are also trials underway investigating methods of improving neuroprotection and reducing cell death after AIS. Nerinetide, a drug that showed promise in pre-clinical models of ischemia and reperfusion was recently investigated and humans [82]. The drug did not seem to improve functioning in those patients who had received tPA but did show a mild treatment effect in those who did not, opening doors for future possibilities for the use of neuroprotection. While stroke creates a tremendous healthcare burden across the world, the plethora of trials currently underway provide hope that this burden will continue to decrease over the next decade.

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