Project Thesis

New developments in the treatment of ischemic stroke patients: a systemic literature

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List of abbreviation

ACA	Anterior cerebral artery
AF	Atrial fibrillation
AHA/ASA	American heart association /American stroke association
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid or aspirin
ASPECT	Alberta stroke program early computed tomography score
BP	Blood pressure
CMBs	Cerebral microbleeds
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
DHC	Decompressive hemicraniectomy
DOAC	Direct oral anticoagulation
DVT	Deep venous thrombosis
DVT	Deep venous thrombosis
DWI	Diffusion weighted imaging
FLAIR	Fluid-attenuated inversion recovery
ICA	Internal carotid artery
ICH	Intracranial haemorrhage
INR	International normalized ratio
IPC	Intermittent pneumatic compression
IV	Intravenous
LDL-C	Low density lipoprotein-cholesterol
LMWH	Low molecular weight heparin
LVO	Large vessel occlusion
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
mTICI score	Modified treatment in cerebral ischemia score
NIHSS	National institutes of health stroke scale
NNCT	Non-contrast computed tomography
NPO	Nil per os
PFO	Patent foramen ovale
PT	Prothrombin time
RCT	Randomized clinical trial
rt-PA	Recombinant tissue plasminogen activator
SBP	Systolic blood pressure
sICH	Symptomatic intracranial haemorrhage

Abstract

The aim of this thesis is to provide medical students with updated knowledge about the current treatment of ischemic stroke. It will focus on four main topics: brain imaging in acute phase, treatment of ischemic stroke, treatment of complications, and secondary prophylaxis. Brain imaging methods in acute phase are non-contrast computed tomography (NCCT) or magnetic resonance imaging (MRI) to exclude cerebral bleeding before administration of intravenous (IV) alteplase and computed tomography angiography (CTA) or magnetic resonance angiography (MRA) to detect large vessel occlusion (LVO) in the anterior circulation in patients who can be treated with mechanical thrombectomy. Choosing between computed tomography (CT) and magnetic resonant imaging (MRI) is mainly dependent on the availability of those methods and the time from symptom onset.

Actual treatment of ischemic stroke includes thrombolysis and mechanical thrombectomy. Both therapies are highly time dependent and should be started as quickly as possible. Thrombolysis is intravenous administration of a recombinant tissue plasminogen activator (rt-PA)/ IV alteplase within 4.5 hours from symptom onset. This is the first-line therapy for all ischemic stroke patients who have no active bleeding or are at high risk of developing bleeding. Mechanical thrombectomy is currently reserved for ischemic stroke patients with LVO in the anterior circulation within 24 hours from symptom onset and can only be done in some stroke centres. There are many specific criteria for selecting eligible patients for thrombolysis and thrombectomy, however patients' individual characteristics should always be evaluated.

The most common complications of ischemic stroke are cerebral edema, dysphagia, and deep venous thrombosis (DVT). Administration of IV alteplase can lead to symptomatic intracranial haemorrhage and angioedema. Treatment for these complications is adequate supportive care, medication, and surgical interventions like hemicraniectomy in patients with severe cerebral edema, percutaneous endoscopic gastrostomy in patients with persistent dysphagia and inferior vena cave filter insertion in patients with DVT.

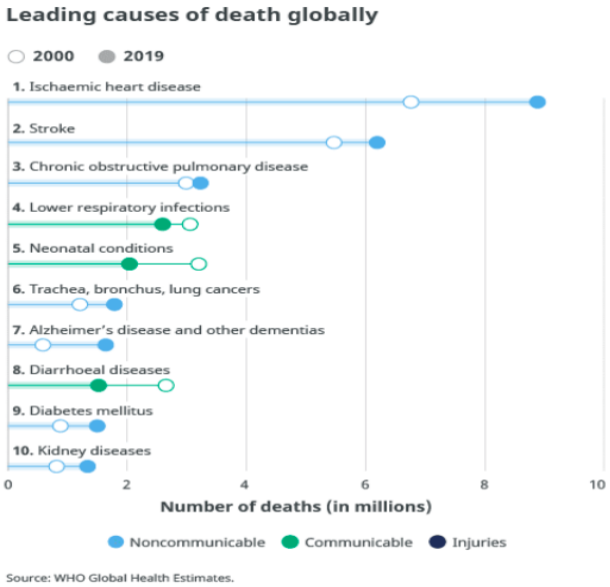
Secondary prophylaxis includes antithrombosis therapy and reducing modifiable risk factors such as, hypertension, dyslipidaemia, diabetes, smoking and physical inactivity. Antithrombosis therapy includes antiplatelet therapy, anticoagulant therapy, or a combination of both. Antiplatelet therapy is preferred in noncardioembolic stroke patients, while cardioembolic stroke patients are treated with anticoagulant agents. Patients who have had ischemic stroke should keep their blood pressure (BP) under control. Goal BP is <130/80 mmHg for those who have risk factors and 140/90 mmHg for those who have no other risk factors. The choice of drug is similar as in other hypertensive patients. However, betablocker is not recommended. Lipid lowering therapy is recommended in all ischemic stroke patients. A high-intensity statin therapy should be applied to achieve low density lipoprotein-cholesterol (LDL-C) < 70mg/dl (1.8 mmol/L). All AIS patients should be screened for diabetes. In diabetes patients, a glycated haemoglobin A1c level of ≤ 7 percent should be maintained by diet, exercise, oral hypoglycaemic drugs, and insulin. AIS patients are also encouraged to quit smoking and do regular exercise to prevent recurrent stroke.

Introduction

Medical students base their knowledge about treatment of ischemic stroke mainly on medical textbooks which are normally 5 to 10 years old, the data in those books is even older (1). In addition, because of the heavy study program, most medical students do not have time to keep up with the new developments. This thesis aims to supply them with the most important and current knowledge about ischemic stroke treatment.

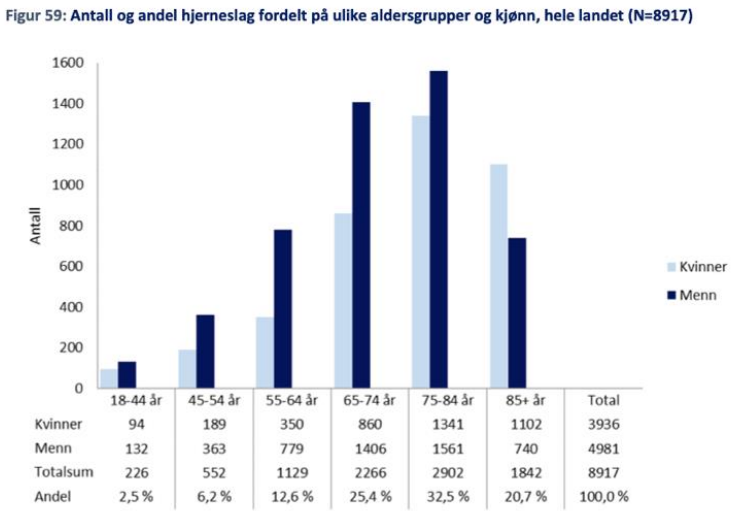
Brain stroke is one of the most common and serious health issue globally. It is the second cause of death and the third reason leading to serious disability (2).

Figure 1 (2)



The Norwegian rapport-2020 shows that brain stroke is highest in group of patients from 75 to 84 years of age and men are more vulnerable than women (3).

Figure 2 (4)



	18-44 år	45-54 år	55-64 år	65-74 år	75-84 år	85+ år	Total
Kvinner	94	189	350	860	1341	1102	3936
Menn	132	363	779	1406	1561	740	4981
Totalsum	226	552	1129	2266	2902	1842	8917
Andel	2,5 %	6,2 %	12,6 %	25,4 %	32,5 %	20,7 %	100,0 %

The majority (85 percent) is ischemic stroke also called brain infarction and other 25% is cerebral haemorrhage (1,3,5). Ischemic stroke is an emergency condition where the blood supply to one or several parts of the brain is blocked by blood clots. This affects brain functions acutely and may lead to irreversible brain damage or mortality if the patient is not treated quickly and adequately (1,5).
All suspected ischemic stroke patients should be transported as quickly as possible to a stroke unit or a stroke centre (1,5,6,7). There is clear evidence that stroke units reduce disability and mortality in both short and long term (1,6). The concept of treatment used in this thesis is based on current practises in stroke centres. We will not discuss what happens to patients prehospital and after discharge.
The Norwegian Directorate of health gives a definition of a stroke unit as follow: A stroke unit is an organized treatment of stroke patients in a geographically delimited ward with fixed beds, staffed with interdisciplinary specially trained health care providers and with a standardized program for diagnostics, observation, acute treatment, early mobilization, and rehabilitation (6). The Norwegian internal medicine book enumerates functions of a stroke unit which includes monitoring and stabilizing vital functions, treating ischemic stroke patients with thrombolysis and arterial thrombectomy, preventing and treating complications, early mobilization, and starting secondary prevention (1).
Based on those definitions, we will in this thesis focus specifically on the following:

- Brain imaging in acute diagnostic
- Treatment of infarction
- Treatment of complications
- Secondary prophylaxis

Brain imaging is very important in ischemic stroke diagnostic and must be done before starting any specific ischemic treatments (7). Most medical students know that we are using CT and MRI to diagnose ischemic stroke, but the details about practical utilization of these neuroimaging methods is often missing (1). The thesis will settle light in this area to give medical students a better insight into current brain imaging techniques.
The actual treatment of brain infarction is revascularization. It is removing blood clots to restore blood supply to the brain. There are two effective methods of revascularization, thrombolysis and mechanical thrombectomy. Both treatments need to be started early after symptom onset (<4.5 hours for thrombolysis and <24 hours for thrombectomy). There are several different criteria for selecting eligible patients. However, it is recommended that patients' individual characteristics should always be evaluated. Patients with severe comorbidities prior to stroke onset or life expectancy less than six months are unlikely to benefit from revascularization. In addition, mechanical thrombectomy can only be done in some stroke centres leading to a low number of ischemic patients treated with thrombectomy. In Norway 21% of ischemic patients received thrombolysis and only 5,3% received thrombectomy in 2020 (3). This thesis will focus on the new developments in thrombolysis and mechanical thrombectomy.
More than 50% of ischemic stroke patients develop one or more complications during the first week. The most serious complication of ischemic stroke is cerebral oedema/brain swelling, which increases intracranial pressure and, in some cases, leads to mortally brain herniation (1). Other common complications are swallowing problem (dysphagia) which can cause aspiration and pulmonary pneumonia, deep vein thrombosis (DVT) can lead to pulmonary embolism and sudden death (7). Revascularization by IV alteplase is also associated with complications such as symptomatic intracranial haemorrhage and orolingual

angioedema (7). In this thesis we will focus on the currently available treatments for these complications.
About 30% of ischemic stroke patients will develop recurrent brain infarction during the first 5 years after the first stroke event. With good secondary prophylaxis can this number reduced by 80% (1). The secondary prophylaxis includes mainly of antithrombotic therapy and reducing modifiable risk factors. The thesis will supply medical students with the most currently recommendations and therapies for secondary prophylaxis in ischemic stroke patients.

Methods

The first knowledge about ischemic stroke was based on the Norwegian internal medicine book (Indremedisin II book -2017), which was used by all medical students in Norway. This book gave medical students basic knowledge about ischemic stroke. The next sources were guidelines for the treatment of acute ischemic stroke (the Norwegian guidelines and the guidelines from American Heart Association/American Stroke Association (AHA/ASA)). They were established by national and international health organizations and updated after 2017. Findings from these sources were used to elaborate on the 4 different separate topics:

1. Brain imaging in acute diagnostic
2. Treatment of infarction
3. Treatment of complications
4. Secondary prophylaxis

Each main topic was further divided in to two parts:
- The new developments
- Overview about the current treatment/recommendations

These findings were then supplied by new findings from UpToDate, Medscape, Neurologic clinic, and other reliable sources. Key words and phrases used to find relevant articles form those sources are, as example: Ischemic stroke treatment, brain imaging in acute ischemic stroke, thrombolysis, thrombectomy, complications of ischemic stroke, etc.
The most practical information from each source was evaluated and compared with findings from previous sources.
National institute of health stroke scale (NIHSS) and modified Rankin scale (mRS) are two common rating scales which are used to evaluate and select ischemic stroke patients for suitable treatments.
NIHSS (table 1) is a 34-point stroke scale that allows quantification of neurologic impairment. This scale provides insight into the location of vascular lesions, is correlated with outcomes for ischemic strokes, and identifies patients who are candidates for thrombectomy. Points are assigned based on performance in six major areas: level of consciousness, visual functions, motor function, sensation, cerebellar function, and language. The scale is used at the initial presentation and can be repeatedly employed over the hospital course to assess the evolution of the patient's neurologic status. Patients with minor stroke usually have a score of less than 5 (8). It is also important to understand limitations of the NIHSS. The scoring paradigm is heavily weighted toward left MCA infarcts. A patient can have a disabling posterior cir- culation stroke, but have a low score because the NIHSS does not quantify symptoms of posterior circulation strokes such as axial ataxia, dysphagia, and diplopia. (9)

Table 1 (7): National Institute of Health Stroke Scale

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—Alert
		1—Drowsy
		2—Obtunded
		3—Coma/unresponsive
1B	Orientation questions (2)	0—Answers both correctly
		1—Answers 1 correctly
		2—Answers neither correctly
1C	Response to commands (2)	0—Performs both tasks correctly
		1—Performs 1 task correctly
		2—Performs neither
2	Gaze	0—Normal horizontal movements
		1—Partial gaze palsy
		2—Complete gaze palsy
3	Visual fields	0—No visual field defect
		1—Partial hemianopia
		2—Complete hemianopia
		3—Bilateral hemianopia
4	Facial movement	0—Normal
		1—Minor facial weakness
		2—Partial facial weakness
		3—Complete unilateral palsy
5	Motor function (arm)	0—No drift
	a. Left	1—Drift before 10 s
	b. Right	2—Falls before 10 s
		3—No effort against gravity
		4—No movement
6	Motor function (leg)	0—No drift
	a. Left	1—Drift before 5 s
	b. Right	2—Falls before 5 s
		3—No effort against gravity
		4—No movement
7	Limb ataxia	0—No ataxia
		1—Ataxia in 1 limb
		2—Ataxia in 2 limbs
8	Sensory	0—No sensory loss
		1—Mild sensory loss
		2—Severe sensory loss
9	Language	0—Normal
		1—Mild aphasia
		2—Severe aphasia
		3—Mute or global aphasia
10	Articulation	0—Normal
		1—Mild dysarthria
		2—Severe dysarthria
11	Extinction or inattention	0—Absent
		1—Mild loss (1 sensory modality lost)
		2—Severe loss (2 modalities lost)

Adapted from Lyden et al.[74] Copyright © 1994, American Heart Association, Inc.

Modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale runs from 0-6, running from perfect health without symptoms to death (10):

0: No symptoms.

1: No significant disability. Able to carry out all usual activities, despite some symptoms.

2: Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3: Moderate disability. Requires some help, but able to walk unassisted.

4: Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5: Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6: Dead.

Results

1. Brain imaging in acute diagnostic

The purpose of neuroimaging in acute phase (first 24 hours) is excluding cerebral hemorrhage, excluding stroke mimics, detecting occlusion in large cervical and intracranial arteries (LVO), estimating the irreversibly infarcted brain tissue (infarct core) and the potentially salvageable brain tissue (penumbra) (11).

The new developments in acute brain imaging

NCCT is adequate for acute ischemic diagnostic and selecting eligible patients for thrombolysis within 6 hours from symptom onset

In the newest guidelines for the early management of patients with acute ischemic stroke-2019, the AHA/ASA state that the diagnosis of ischemic stroke can be made accurately based on the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in most patients with careful attention. They based their statement on the result from the NINDS rt-PA trial (National Institute of Neurological Disorders and Stroke) (12) and the ECASS III trial (European Cooperative Acute Stroke Study III) (13), which used only NNCT neuroimaging modality. These two trials also provide the basis for the new recommendations that IV alteplase administration in eligible patients should started without first obtaining MRI to exclude cerebral microbleeds (CMBs) and should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging (7).

NCCT, a type of X-ray device to make cross-sectional images, is currently the most suitable neuroimaging method in acute phase (1,6,7). NCCT is no sensitive in detecting ischemic stroke during the first 6-12 hours because oedema and infarction have not yet developed enough to be identified. NCCT therefore can neither confirm nor exclude ischemic stroke. It is used in acute phase to exclude cerebral haemorrhage which is a contraindication for thrombolytic therapy (14).

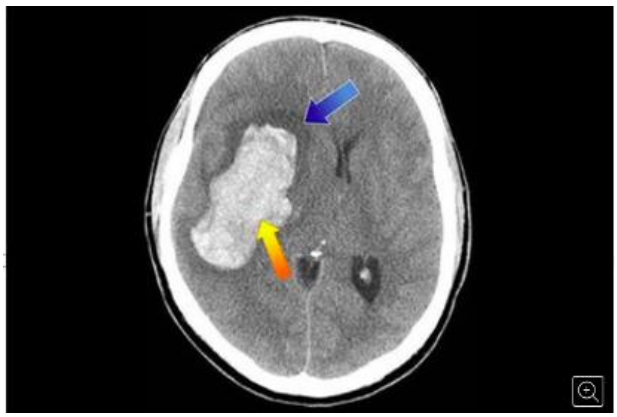


Figure 3 (14): This CT scan reveals an intraparenchymal haemorrhage (orange arrow) with surrounding oedema (blue arrow)

NCCT is preferred over all other imaging methods because of its widespread access, speed of acquisition and excellent in showing bleeding (11). The Norwegian guideline recommends that NCCT should be done within 15 minutes after arriving to the hospital (6). If NCCT is negative for intracranial haemorrhaged /ICH, time from symptom onset is less than 4,5 hours and the patient do not have contraindications for thrombolysis, IV alteplase should be started as quickly as possible (1,6,7,11).

Even though NCCT is not as good as other neuroimaging methods in detecting early sign of infarction, extensive regions of clear hypoattenuation on NCCT (figure 4) is associated with irreversible injury, which is a contraindication for thrombolysis because these patients have poor prognosis despite IV alteplase treatment (14). Additionally, NCCT can sometimes detect LVO (hyperdense vessel sign) and exclude stroke mimics, such as brain tumour, aneurism, cranial bone fracture, and hydrocephalus which are very useful in assessment of the patient in acute phase (11,14).

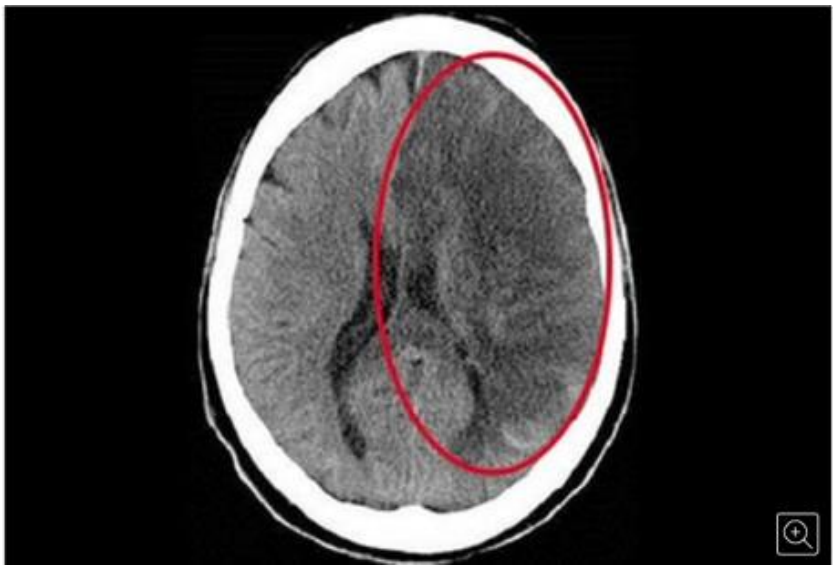


Figure 4 (14): The CT scan demonstrates extensive hypodensity and sulcal effacement involving the left anterior cerebral artery (ACA) and MCA territories, consistent with large acute infarction. Scattered curvilinear areas of hyperdensity are apparent, suggestive of developing petechial haemorrhage in this sizeable area of infarction.

DWI-FLAIR mismatch is useful in selecting eligible patients for thrombolysis when the time from symptom onset is unclear

The AHA/ASA guidelines-2019 also recommend using MRI to identify DWI-FLAIR mismatch when selecting AIS patients, who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state, for thrombolysis (7).
The DWI-FLAIR mismatch (figure 5) refers to evidence of a hyperintense lesion on diffusion weighted imaging (DWI) consistent with acute infarction but no corresponding signal abnormality on the Fluid-attenuated inversion recovery (FLAIR) images. This mismatch indicates that the stroke is relatively acute (< 4.5 hours), since insufficient time has passed for development of hyperintense signal on FLAIR (11).

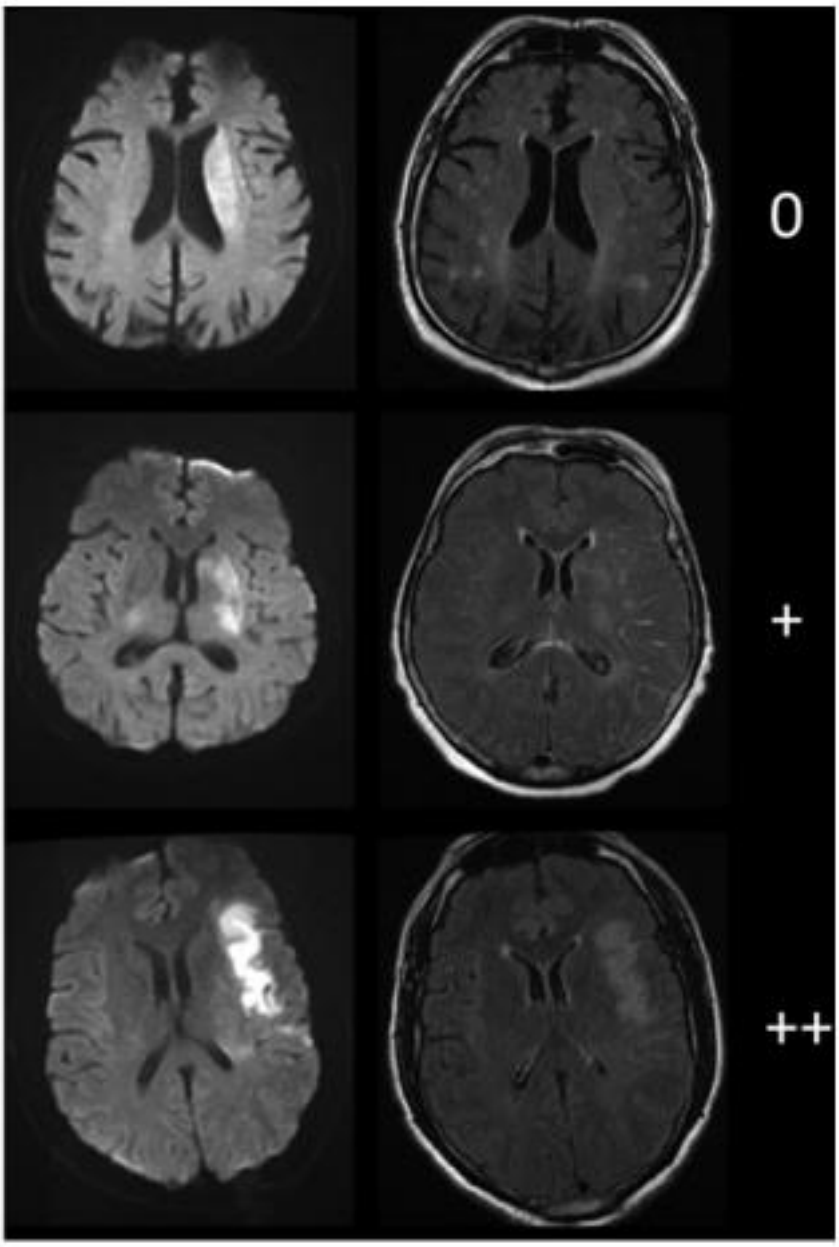


Figure 5 (15): Diffusion-weighted imaging (left) and fluid-attenuated inversion recovery imaging (right) examples of visual gradings. Intralesional fluid-attenuated inversion recovery hyperintensities were graded as absent (0), subtle (+), or obvious (++)

The new recommendation is based on the WAKE-UP trial (16), which used DWI-FLAIR mismatch as an eligibility criterion. In addition, DWI lesions larger than one-third of the territory of the middle cerebral artery (MCA), NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. The end point of an mRS score of 0 to 1 at 90 days was achieved in 53.3% of the IV alteplase group and in 41.8% of the placebo group (*P*=0.02) (7,15).
Some institutions have created rapid MRI protocol with limited sequences, such as DWI, FLAIR, apparent diffusion coefficient and gradient echo, or susceptibility-weighted imaging, to rapid assess these patients for thrombolysis (9).

CTA or MRA is adequate in selecting patients for thrombectomy within 6 hours from symptom onset

Another new recommendation from the AHA/ASA guideline-2019 is: When evaluating patients with AIS within 6 hours of last known normal with LVO and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6, selection for mechanical thrombectomy based on CT and CTA or MRI and MRA is recommended in preference to performance of additional imaging such as perfusion studies (7).

ASPECTS method (figure 6) is a simple and reliable way to assess early ischemic changes. It was traditionally scored on NCCT, however, greater accuracy for detection of ischemic change and identifying final infarct volume can be achieved when it is scored on CTA source images (9).

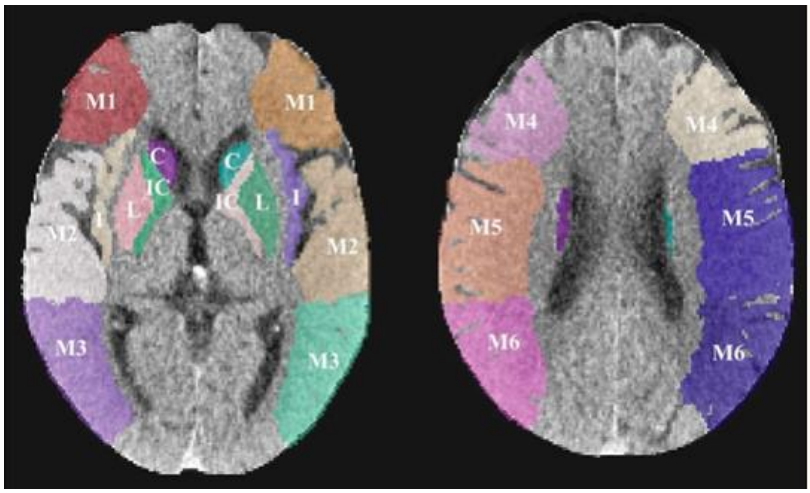


Figure 6 (9): Example of each ASPECT region. L: Lentiform, C: Caudate, IC: Internal capsule, M: MCA

The ASPECTS value is calculated from evaluation of two standard axial NCCT images: one at the level of the thalamus and basal ganglia, and one just rostral to the basal ganglia. The score divides the middle cerebral artery (MCA) vascular territory into 10 regions of interest that are evaluated on these two axial cuts. When calculating the ASPECTS value, one point is subtracted for early ischemic change, such as focal swelling or parenchymal hypoattenuation, in each of the 10 defined regions. Therefore, a normal NCCT has an ASPECTS value of 10 points, while diffuse ischemic change throughout the MCA territory gives a value of zero. Since ASPECTS is limited to the MCA territory, ASPECTS is not applicable to stroke outside of the MCA territory, such as lacunar or brainstem stroke. (11).

This new recommendation from AHA/ASA was based on 2 randomized clinical trials (RCTs) which demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed <6 hours from stroke onset (17,18). Because these trials required only NCCT and demonstration of LVO, the role of additional imaging-based eligibility criteria is not well established and could lead to the exclusion of patients who would benefit from treatment and are therefore not indicated at this time (7).

Perfusion imaging is useful in selecting patients for thrombectomy within 6 to 24 hours from symptom onset

The AHA/ASA guidelines-2019 recommend obtaining CTP or DW-MRI, with or without MRI perfusion when selecting eligible patients who have LVO in the anterior

circulation for mechanical thrombectomy within 6 to 24 hours of last known normal, but only when patients meet DAWN or DEFUSE 3 eligibility criteria (7).
The DAWN trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) used clinical-core mismatch (a combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal (19). This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%)(7).
The DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial used perfusion-core mismatch and maximum core size on CTP or DW-MRI as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy (19). This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%). DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection in clinical practice (7).

CTA before obtaining serum creatinine in patients without history of renal impairment
Based on analyses from several observational studies which suggest that the risk of contrast induced nephropathy secondary to CTA imaging is relatively low, particularly in patients without a history of renal impairment, waiting for these laboratory results may lead to delays in mechanical thrombectomy. The AHA/ASA guidelines recommend CTA before obtaining serum creatinine in patients with no history of renal impairment, who otherwise meet criteria for mechanical thrombectomy (7).

Imaging of extracranial carotid, vertebral arteries and collateral flow status is useful in thrombectomy planning
Knowledge of vessel anatomy and presence of extracranial vessel dissections, stenoses, and occlusions may assist in planning endovascular procedures or identifying patient's ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature. The AHA/ASA guidelines recommend that in patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, may be reasonable to provide useful information on patient eligibility and endovascular procedural planning (7).
In addition to imaging of extra carotid and vertebral arteries, collateral flow status is also useful in selecting patients and planning of thrombectomy (7). The ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), using multiphase CTA to select patients with moderate to good collateral circulation for mechanical thrombectomy up to 12 hours from onset, was stopped early for efficacy (20). Acquisition of advanced imaging however should not delay door–to–groin puncture times (7).

Current recommendations about brain imaging in acute phase

In general, there is a unanimous opinion about using brain imaging in acute phase between medical sources, as following:
- All patients with suspected acute stroke should receive emergency brain imaging evaluation on first arrival to a hospital before initiating any specific therapy to treat acute ischemic stroke (1,6,7).

- Systems should be established so that brain imaging studies can be performed as quickly as possible in patients who may be candidates for IV fibrinolysis or mechanical thrombectomy or both (1,6,7).
- For suspected ischemic stroke patients who have time from clear symptom onset < 4.5 hour, NNCT or MRI is recommended in acute phase to quickly exclude cerebral bleeding and select eligible patients for thrombolysis (1,6,7,11).
MRI is recommended as an alternative brain imaging for NCCT in the acute phase (1,6,7,11) because it is not as widely available as NNCT and in practice MRI is more limited by contraindications or patient intolerance than CT (11). Standard brain MRI protocols include conventional T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and T2*-weighted gradient-recalled echo (GRE) sequences along with diffusion-weighted imaging (DWI) (11). Susceptibility weighted imaging (SWI) is also an magnetic resonance imaging technique that exploits the magnetic susceptibility differences of various compounds, such as blood, iron, and diamagnetic calcium, thus enabling new sources of MR contrast (21). Both GRE and SWI are as good as NCCT at excluding cerebral haemorrhage. DWI (figure 7) is better than NCCT in detecting early infarction (DWI can detect injury with 15-30 minutes of symptom onset) and exclusion other stroke mimics (11).
- For suspected ischemic stroke patients who awake with stroke, MRI to identify diffusion-positive FLAIR-negative lesions (DWI-FLAIR mismatch) is recommended to select patients for treatment with intravenous thrombolysis (1,6,7,11).

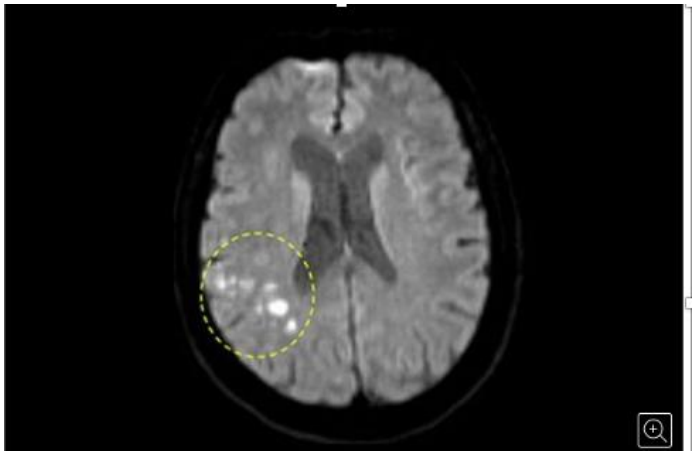


Figure 7 (14): The diffusion-weighted imaging (DWI) scan demonstrates multiple small areas of restricted diffusion in the right parietal lobe, which are consistent with ischemia in the right MCA territory.

- In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT perfusion and MRI perfusion imaging (6,7).
- For ischemic stroke patients who have time from clear symptom onset < 6 hours, CTA or MRA is recommended in acute phase to detect LVO in the anterior circulation and select eligible patients for mechanical thrombectomy (6,7,11).
The main purpose of CTA in acute phase is detecting and evaluating LVO in the anterior circulation in patients who can be treated with mechanical thrombectomy within 6 hours from symptom onset (6,7,11). The Norwegian national guideline recommends that CTA should be done right after NCCT in acute phase, but this should not delay thrombolysis if the patient is also eligible for it (6). CTA is a CT scan with venous contrast injection to make blood vessels more visible. Blood Clot causes a filling defect which can be seen on the source images. CTA

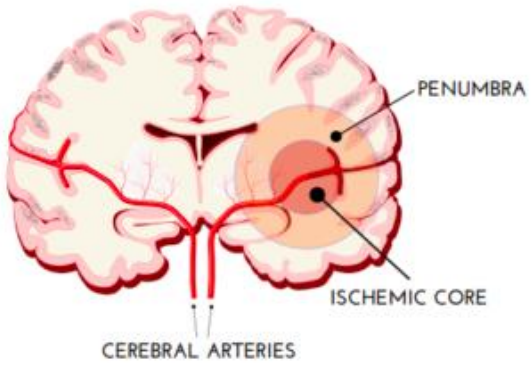
source images are also more sensitive than NCCT for the detection of early brain infarction. Hypoattenuation on CTA source images correlates with brain infarction and cytotoxic edema on diffusion-weighted MRI (DWI) (11). CTA and MRA perform well at identifying large vessel occlusion, but CTA has added benefits of speed and good spatial resolution (14).

- CTA imaging before obtaining serum creatinine in ischemic stroke patients who otherwise meet the criteria for thrombectomy and have no history of kidney disease is recommended (7).
- Administration of IV alteplase in eligible patients without first obtaining MRI to exclude cerebral microbleeds (CMBs) is recommended (7).
- When evaluating ischemic stroke patients within 6 hours of last known normal with LVO and an ASPECTS score ≥6, selection for mechanical thrombectomy based on CT and CTA or MRI and MRA is recommended in preference to performance of additional imaging such as perfusion studies (7).
- For ischemic stroke patients with LVO in the anterior circulation, who wake up with stroke or have time from clear symptom onset within 6 to 24 hours, CTA with CTP or MRA with DW-MRI with or without MRP is useful for selecting eligible patients for mechanical thrombectomy (6,7,11).
- In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, may be reasonable to provide useful information on patient eligibility and endovascular procedural planning (7).
- It may be reasonable to incorporate collateral flow status into clinical decision-making in some candidates to determine eligibility for mechanical thrombectomy (7).

2. Treatment of infarction

Each cerebral infarction has a core and an area surrounding the core (penumbra) (1,22)

Figure 8 (22)



Brain cells in the core receive blood supply less than 10 ml/100g brain tissue/minute and usually die before patient is brought to the hospital. Brain cells in penumbra however have blood supply more than 10 ml/100 g brain tissue/minute and can still be alive several hours after onset of stroke symptom. The purpose of infarction treatment is to rescuer those penumbra cells by revascularization (1).

Currently, there are two improve methods of revascularization, intravenous thrombolysis and mechanical thrombectomy (1,6,7). Other therapies such as intra-arterial fibrinolysis initiated

within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of IV alteplase might be considered, but the consequences are unknown (7).

Thrombolysis

The new developments in thrombolysis:

Wake up ischemic stroke patients can receive thrombolysis

As mentioned above in the brain imaging part of this thesis, DWI-FLAIR mismatch has been approved by WAKE-UP trial to be useful in selecting eligible patients who wake up with stroke or have unclear time from symptom onset, for thrombolysis. In this trial, patients with DW-MRI lesions larger than one-third of the territory of the middle cerebral artery (MCA), NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all excluded (16).

Following the result from WAKE-UP trial, the AHA/ASA guideline-2019 recommend IV alteplase administration in AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state if they have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR (7).

Mild but disabling ischemic stroke patients can receive thrombolysis within 4.5 hours from symptom onset

The AHA/ASA guidelines-2019 made new recommendations regarding mild (NIHSS 0 to 5) ischemic stroke patients. Those who have mild but disabling stroke, thrombolysis treatment should be started within 4.5 hours from symptom onset or last known to be normal. In contrast, patients who have mild nondisabling stroke, thrombolysis treatment is not recommended (7). This conclusion come from a meta-analysis of 9 trials of IV alteplase in AIS including subjects from the NINDS rt-PA trial and IST-3 trail (International Stroke Trial 3) showed benefit for patients with mild stroke defined as NIHSS score 0 to 4 (23).

In ECASS III, there was no significant interaction of benefit (mRS score 0–1 at 90 days) or safety with stroke severity when patients were categorized by baseline NIHSS score of 0 to 9, 10 to 19, and >20 (13).

In SITS-ISTR (Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry) (24), good functional outcomes (mRS score 0–1 at 90 days) and risk of symptomatic intracranial haemorrhage (sICH) were similar or the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours. Similarly, in the AHA GWTG (Get With The Guidelines) registry , good functional outcomes, mortality, and risk of sICH were the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours. These patients were not further categorized by whether their acute neurological deficits were disabling (7).

New expanded inclusion criteria

Although patients with the following conditions were historically excluded from receiving alteplase, further evidence has shown that IV alteplase is reasonable in patients with (7):

- Sickle cell disease
- Hyperdense MCA sign on baseline CT
- 1 to 10 cerebral microbleeds demonstrated on a prior MRI

No aspirin administration within 90 minutes after the start of IV alteplase

The ARTIS trial (Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke) compared the effects of very early addition (within 90 minutes) of 300 mg IV aspirin to alteplase with standard treatment with alteplase without IV aspirin. The trial was terminated after 642 of the 800 targeted patients had been enrolled because IV aspirin was associated with an increased risk of symptomatic intracranial hemorrhage (4.3% versus 1.6%

in the standard treatment group, and no difference in the rate of favorable functional outcome (mRS score 0–2) at 3 months (54.0% of patients in the aspirin group versus 57.2% of patients in the standard treatment group (25)
The AHA/ASA guidelines-2019 recommend that in patients who are eligible for thrombolysis, administration of ASA should begine 24 hours after administration of IV alteplase started. No aspirin should be administered during thrombolytic therapy and 90 minutes after the start of IV alteplase (7).

Tenecteplase before endovascular therapy
Although intravenous alteplase is currently the only agent approved by the United States Food and Drug Administration for the treatment of acute ischemic stroke, a second fibrinolytic, tenecteplase, may be as effective. Tenecteplase is a variant of alteplase bioengineered to have higher fibrin specificity and increased resistance to plasminogen activator inhibitor-1, and is administered via a single intravenous bolus (9).
The AHA/ASA guidelines-2019 recommend choosing tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy (7).
This new recommendation was based on the EXTEND-IA TNK trail (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) which investigated intravenous tenecteplase, 0.25 mg/kg as a single bolus, versus intravenous alteplase at standard dosing in patients presenting within 4.5 hours of symptom onset and eligible for endovascular therapy (26). The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrieval thrombus at the time of the initial angiographic assessment. This primary outcome was reached in 22% of the tenecteplase treated patients versus 10% of those treated with alteplase. The tenecteplase group had a median mRS of 2 at 90 days versus a median mRS of 3 in the alteplase group (7).
An obvious critique of this trial is that the primary outcome was a radiologic outcome and not a clinical one (9). A follow-up open-label trial comparing 2 doses of tenecteplase (0.4 mg/kg and 0.25 mg/kg) in patients with ischemic stroke due to large vessel occlusion did not find a radiographic or clinical advantage of the higher dose (7,9).

Tenecteplase in patients with minor neurological impairment and no major intracranial occlusion
The AHA/ASA guidelines-2019 recommend that Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion (7).
In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion (27). Because of the shorter time to prepare and administer tenecteplase and the lack of requirement for an IV infusion pump during interfacility transfer, some institutions have adopted its use (8).

Sonothrombolysis as adjuvant therapy with iv fibrinolysis is not recommended
The AHA/ASA guidelines-2019 recommend not using sonothrombolysis as adjuvant therapy with iv fibrinolysis. This new recommendation was based on the result from 2 RCTs. The NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis or sham. Neurological improvement at 24 hours and

functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of ICHs (28).
The CLOTBUST-ER trial (Combined Lysis of Thrombus with Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke) randomized 676 patients with AIS (NIHSS score ≥10) who received IV alteplase within 3 or 4.5 hours of symptom onset and randomly allocated to operator independent sonothrombolysis or sham ultrasound. Compared with the control arm, the neurological improvement, death, and serious adverse events in the intervention arm were not statistically different (29). At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV fibrinolysis (7).

Telestroke/teleradiology evaluations of AIS patients can be effective for correct IV alteplase eligibility decision making.
The STRokEDOC (Stroke Team Remote Evaluation Using a Digital Observation Camera) pooled analysis supported the hypothesis that telemedicine consultations, which included teleradiology, compared with telephone-only resulted in statistically significantly more accurate IV alteplase eligibility decision-making for patients exhibiting symptoms and signs of an acute stroke syndrome (30).

Administration of IV alteplase guided by telestroke consultation for patients with AIS can be beneficial.
A systematic review and meta-analysis was performed to evaluate the safety and efficacy of IV alteplase delivered through telestroke networks in patients with AIS. indicate that IV tPA delivery through telestroke networks is safe and effective in the 3-hour time window. sICH rates were similar between patients subjected to telemedicine- guided IV alteplase and those receiving IV alteplase at stroke (31)

Current recommendations about thrombolysis

Overview: - Thrombolysis is an intravenous administration of a recombinant tissue Plasminogen activator (rt-PA)/ IV Alteplase to revascularize the blocked cerebral blood vessel and restore blood flow to the brain. This is the first-line treatment of ischemic stroke and should be started as quickly as possible in patients who meet eligibility criteria. Thrombolysis therapy gives the best result when applied within 3 hours of symptom onset, but the time-window can be extended to 4.5 hours (1,6,7,32).
The alteplase dose is calculated at 0.9 mg/kg of actual body weight, with a maximum dose of 90 mg. Ten percent of the dose is given as an intravenous bolus over one minute and the remainder is infused over one hour (6,7,32).
In Norway, recombinant tissue plasminogen activator (rt-PA)/ IV alteplase is the only improve medicine for thrombolytic therapy (1,6). In contrast, the AHA/ASA guideline suggests choosing Tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy or tenecteplase administered as a 0.4-mg/kg single IV bolus as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion. They do not recommend administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase (7).
NCCT brain imaging is the only required acute neuroimaging method before administration of IV alteplase. In patients who wake up with stroke or have unclear time of symptom onset, MRI with DWI-FLAIR mismatch can be useful to selecting eligible patients for thrombolysis. Because benefit of thrombolytic therapy is time dependent, treatment should be

initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT perfusion and MRI perfusion imaging (7).

Criteria: - General eligible criteria for thrombolysis are that the patient has a clinical ischemic stroke diagnosis causing measurable neurologic deficit (NIHSS >5), time from symptom onset or last known of normal is <4.5 hours, NCCT shows no intracranial haemorrhage (ICH), and patients are not at high risk of developing bleeding (1,6,7,32).

The AHA/ASA guideline 2019 announced the following exclusion criteria for thrombolysis treatment (7):

- Mild nondisabling stroke: NIHSS score 0-5
- CT brain imaging exhibits extensive regions of clear hypoattenuation. (Severe hypoattenuation defined as obvious hypodensity represents irreversible injury. These patients have a poor prognosis despite IV alteplase)
- CT brain imaging reveals an acute intracranial haemorrhage
- Ischemic stroke within 3 months
- Severe head trauma within 3 months
- Acute head trauma (posttraumatic infarction that occur during the acute in-hospital phase)
- Intracranial/intraspinal surgery within 3 months
- History of intracranial haemorrhage
- Subarachnoid haemorrhage
- GI malignancy or GI bleeding within 21 days
- Coagulopathy: platelets < 100 000/mm^3, INR>1.7, aPTT > 4, PT >15s.
- Patients who have received a full treatment dose of LMWH within the previous 24 hours.
- Patients who have received direct thrombin inhibitors or direct factor Xa inhibitors within the previous 48 hours.
- Infective endocarditis
- Aortic arch dissection
- Intra-axial intracranial neoplasm

Supportive care: - For patients who otherwise are eligible for thrombolysis, blood pressure should be at or below 185/110 mmHg before, during and 24 hours after alteplase administration. Patients with blood pressure higher than 185/110 mmHg can be treated with Labetalol to reduce blood pressure to the goal level (6,7,32).

Blood glucose must always be checked and corrected before IV alteplase administration because both hypoglycaemia and hyperglycaemia can mimic stroke. Hypoglycemia (blood glucose <60 mg/dL equal to 3.3 mmol/L) should be treated, and blood glucose should be between 140-180 mg/dl equal to 7.8-10 mmol/L (6,7).

Baseline electrocardiographic assessment is recommended in patients presenting with AIS but should not delay initiation of IV alteplase (7).

Blood sample can be withdrawn but IV alteplase should not be delayed while waiting for hematologic or coagulation result if there is no reason to suspect an abnormal test (6,7).

Antiplatelet therapy should be started for most patients 24 to 48 hours after thrombolytic therapy (6,7,32).

Symptomatic intracranial haemorrhage: - Treatment with IV alteplase is associated with increased early risk of intracerebral haemorrhage which happens in 5 to 7% of ischemic stroke patient (32).

Symptomatic intracerebral hemorrhage should be suspected in any patient who develops sudden neurologic deterioration, a decline in level of consciousness, new headache, nausea

and vomiting, or a sudden rise in blood pressure after thrombolytic therapy is administered, especially within the first 24 hours of treatment (32).
Management of symptomatic intracranial haemorrhage includes, stop alteplase infusion, order brain NCCT or MRI to detect/confirm cerebral haemorrhage, take a blood test (for typing, cross matching, and measurement of prothrombin time, activated partial thromboplastin time, platelet count, and fibrinogen), administration of agents to reverse the effects of thrombolytic therapy and antithrombotic therapy (7,32).
Systemic bleeding: - Mild systemic bleeding usually occurs in the form of oozing from intravenous catheter sites, ecchymoses (especially under automated blood pressure cuffs), and gum bleeding; these complications do not require cessation of IV alteplase treatment. More serious bleeding, such as from the gastrointestinal or genitourinary system, may require discontinuation of alteplase depending on the severity. Rarely, patients who suffer stroke after a recent myocardial infarction can develop bleeding into the pericardium, resulting in life-threatening tamponade. Consequently, patients who become hypotensive after alteplase should be evaluated with urgent echocardiography (32).
Angioedema: - Orolingual angioedema occurs in 1 to 8 percent of patients treated with alteplase for ischemic stroke, and it is typically mild, transient, and contralateral to the ischemic hemisphere. Patients taking angiotensin converting enzyme inhibitors and those with CT evidence of ischemia in the frontal and insular cortex may be at increased risk. Severe orolingual angioedema is rare but may cause partial airway obstruction and require emergent management, which includes intubation, discontinue alteplase infusion and hold angiotensin converting enzyme inhibitor. If there is further increase in angioedema, give epinephrine (0.1 percent) 0.3 mL subcutaneously or 0.5 mL by nebulizer, but note that epinephrine has a theoretical risk of blood pressure elevation and hemorrhage. Additional treatment options for refractory angioedema include Icatibant and plasma-derived, C1 inhibitor concentrate which have been used to treat hereditary angioedema and angiotensin converting enzyme inhibitor-related angioedema (32).

Mechanical thrombectomy

The new developments in mechanical thrombectomy

Direct aspiration thrombectomy as first-pass mechanical thrombectomy

The AHA/ASA guidelines- 2019 state that direct aspiration thrombectomy as first-pass mechanical thrombectomy is recommended as noninferior to stent retriever for patients who meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS ≥6; and (6) treatment initiation (groin puncture) within 6 hours of symptom onset (7).
This statement was based on the COMPASS trial which was successfully demonstrated that aspiration thrombectomy is noninferior compared with stentriever thrombectomy in patients who meet criteria as mentioned above (33).
The ASTER trial compared the contact aspiration technique and the standard stent retriever technique as first-line mechanical thrombectomy for successful revascularization within 6 hours among patients with acute anterior circulation ischemic stroke and LVO. This trail used different criteria from COMPASS trial, but its result also demonstrated that aspiration is noninferiror to stent retriever (34).

DEFUSE 3 criteria can select eligible patients for thrombectomy within 6 to 16 hours from symptom onset

The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen

well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%) (19)
Based on this trial, the AHA/ASA guidelines-2019 recommend using DEFUSE 3 criteria to select eligible patients for mechanical thrombectomy (7)

DAWN criteria can select eligible patients for thrombectomy within 6 to 24 hours from symptom onset
The DAWN trial used clinical-core mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in function outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%) (19)
As a result, a new recommendation was made in the AHA/ASA guideline -2019 which recommend using DAWN criteria to select ischemic stroke patients for mechanical thrombectomy within 6 to 24 hours from symptom onset (7)

Mechanical thrombectomy should be started as quickly as possible
In pooled patient-level data from 5 trials (35) the odds of better disability outcomes at 90 days (mRS scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture. Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability and less functional independence (7).

Optimal blood pressure for AIS patients is unknown:
There are many different ideas around blood pressure management in ischemic stroke patients. According the AHA/ASA guidelines-2019 (7):
- Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.
- Patients who have elevated BP and otherwise eligible for treatment with IV alteplase should have their BP carefully lowed so that their SBP is < 185 mmHg and their diastolic BP is <110 mmHg before iv fibrinolytic therapy is initiated.
- In patients for whom mechanical thrombectomy is planned and who have not received iv fibrinolytic therapy, it is reasonable to maintain BP<185/110 mmHg before the procedure.
- In patients who undergo mechanical thrombectomy, it is reasonable to maintain the BP ≤180/105 mmHg during and for 24 hours after the procedure.
- In patients who undergo mechanical thrombectomy with successful reperfusion, it might be reasonable to maintain BP < 180/105 mmHg.
- In patients with BP ≥220/120 mm Hg who did not receive IV alteplase or mechanical thrombectomy and have no comorbid conditions requiring urgent antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.
- In patients with BP <220/120 mm Hg who did not receive IV alteplase or mechanical thrombectomy and do not have a comorbid condition requiring urgent antihypertensive treatment, initiating, or reinitiating treatment of hypertension within the first 48 to 72 hours after an AIS is not effective to prevent death or dependency.
However, the blood pressure level that should be maintained in patient with AIS to ensure the best outcomes is not known (7).
UpToDate suggests systolic blood pressure (SBP) between 150-180 prior to reperfusion. They believe that SBP ≥150 mmHg may be useful to maintain adequate collateral blood flow

during the time the large artery remains occluded, but SBP ≥ 180 mmHg may increase the risk of hemorrhage in ischemic brain regions even when thrombolytic agents are not used. Once reperfusion is achieved with mechanical thrombectomy, SBP should be <140 mmHg (36).

Current recommendations about mechanical thrombectomy

Overview: - Mechanical thrombectomy is another method to revascularize a blocked blood vessel and can be done within 24 hours after symptom onset. This treatment is reserved mainly for ischemic stroke patients who have occlusion in proximal large vessel (LVO) in the anterior circulation (1,6,7,36). The anterior circulation is the blood supply to the anterior portion of the brain which located above the tentorium cerebelli (supratentorial region) excluding the occipital. The anterior circulation includes internal carotid artery (ICA), middle cerebral artery (MCA) and anterior cerebral artery (ACA) (37).
Mechanical thrombectomy is an independent treatment from thrombolysis. Ischemic stroke patients who meet the criteria for thrombolysis should receive it without delaying even though thrombectomy is being considered. Thrombectomy also should be started as early as possible in eligible patients without wating for the result from thrombolytic therapy (6,7,36).
There are a limited number of hospital/ stroke centres which can offer mechanical thrombectomy because the treatment requires expertise in the use of second-generation stent retrievers, a qualified interventional neurologist, and a comprehensive periprocedural care team. There are only 5 specialist stroke units in Norway can offer this treatment (6,36).
A second-generation stent retriever device or a catheter aspiration device is passed though the femoral artery (groin puncture) and follows the artery system to the blood clot and fishes it out (5,56). The use of stent retrievers or aspiration device is recommended in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device (7).
Either monitored anaesthesia care (conscious sedation) or general anaesthesia may be used for procedural sedation during mechanical thrombectomy. The aesthetic technique should be chosen based upon individual patient risk factors, preferences, and institutional experience (7,36).

Criteria within 6 hours:

UpToDate recommends the following criteria which are modified from those used in the MR CLEAR trial (36):

- A clinical diagnosis of acute stroke
- A deficit on the National Institutes of Health Stroke Scale (NIHSS) of ≥ 6 points or any persistent neurologic deficit that is potentially disabling
- An Alberta Stroke Program Early CT Score (ASPECT) score of ≥ 6 points on NCCT or DWI
- Brain CT or MRI scan ruling out intracranial haemorrhage
- Intracranial arterial occlusion of the distal intracranial internal carotid artery (ICA), or the M1 or M2 segments of the middle cerebral artery (MCA), or the A1 or A2 segments of the anterior cerebral artery (ACA), demonstrated with CT angiography, MR angiography, or digital subtraction angiography
- Age ≥18 years

According to the AHA/ASA guideline, mechanical thrombectomy is an improve beneficial method in patients who meet the following criteria (7):

(1) prestroke mRS score of 0 to 1
(2) causative occlusion of the internal carotid artery (ICA) or MCA segment 1 (M1)
(3) age ≥18 years
(4) NIHSS score of ≥6

(5) ASPECTS of ≥6

(6) treatment can be initiated (groin puncture) within 6 hours of symptom onset

However, the AHA/ASA guideline also recommends mechanical thrombectomy treatment in ischemic stroke patients who have occlusion in MCA segment 2 (M2), or MCA segment 3 (M3), anterior cerebral arteries (ACA), vertebral arteries, basilar artery, or posterior cerebral arteries if this treatment can be started within 6 hours of symptom onset although the benefits are uncertain (7).

They also recommend mechanical thrombectomy for patients who have causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1) but do not meet the criteria mentioned above, which mean prestroke mRS score >1, ASPECTS <6, or NIHSS score <6 if the treatment can be started within 6 hours of symptom onset although the benefits are uncertain (7).

The Norwegian guideline states that there are no studies show the different outcome between age groups treated with mechanical thrombectomy. They therefore recommend no age limitation for mechanical thrombectomy in Norway (5). Like the AHA/ASA guideline, they also recommend this treatment for patients with occlusion in large vessels in the anterior circulation and in the basilar artery, even though there is no clear evidence about thrombectomy is also benefit for patients with occlusion in the basilar artery (5).

Criteria beyond 6 hours:

Eligibility criteria based upon the DEFUSE 3 trial for patients who can start treatment (femoral puncture) within 6 to 16 hours of time last known to be at neurologic baseline are as follows (36):

- NIHSS of ≥6 points
- mRS score ≤2
- Arterial occlusion of the cervical or intracranial ICA (with or without tandem MCA lesions) or the M1 segment of the MCA demonstrated on MR angiography or CT angiography
- A target mismatch profile on CT perfusion or MRI defined as an ischemic core volume <70 ml, a mismatch ratio (the volume of the perfusion lesion divided by the volume of the ischemic core) >1.8, and a mismatch volume (volume of perfusion lesion minus the volume of the ischemic core) >15 mL
- Age 18 to 90 years

Eligibility criteria based upon the DAWN trial for patients who can start treatment (femoral puncture) within 6 to 24 hours of time last known to be at neurologic baseline are as follows (36):

- Failed or contraindicated for intravenous alteplase
- NIHSS of ≥10 points
- mRS score ≤1
- Baseline infarct involving less than one third of the territory of the MCA on CT or MRI
- Intracranial arterial occlusion of the ICA or the M1 segment of the MCA
- A clinical-core mismatch according to age:
    - Age ≥80 years: NIHSS ≥10 and an infarct volume <21 mL
    - Age <80 years: NIHSS 10 to 19 and an infarct volume <31 mL
    - Age <80 years: NIHSS ≥20 and an infarct volume <51 mL

UpToDate recommends using clinical-ASPECT mismatch, such as NIHSS ≥10 and ASPECTS ≥6 if stroke centres do not use automated infarct volume determination to select eligible patients for thrombectomy beyond 6 hours from symptom onset (36). However, the

AHA/ASA guidelines-2019 assert that DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice (7).

Brain imaging:

Generally, all suspected ischemic stroke should receive NCCT or MRI initially to exclude cerebral haemorrhage and receive thrombolytic treatment if they meet criteria for it. Then, CTA or MRA is done to detect LVO in the anterior circulation and select eligible patients who benefit from mechanical thrombectomy treatment (6,7,11). CTA or MRA however should not delay thrombolysis treatment if the patient meets criteria for it. As mentioned above, all brain imaging needs to be done as quickly as possible. CTA/MRA imaging should be done before obtaining a serum creatinine concentration in patients who have no history of kidney disease (7). CTA or MRA is also recommended in preference to performance of additional imaging such as perfusion studies (6,7).

In addition to detect LVO in the anterior, CTA or MRA is needed to calculate ASPECT score (ASPECT can be calculated from NCCT but more reliable when it is calculated from CTA or MRA) (36) when selecting eligible patients within 6 hours from symptom onset.

When selecting eligible patients beyond 6 hours from symptom onset (using DAWN and DEFUSE3 criteria), brain imaging is needed to calculate the infarct core volume. Infarct core volume is calculated by an automated infarct volume determination (36). In stroke centres which do not use this automated infarct volume determination, clinical-ASPECT mismatch, such as NIHSS ≥10 and ASPECTS ≥6 can be an alternative (36).

Complications of mechanical thrombectomy: - Mechanical thrombectomy is not associated with increased rates of symptomatic intracranial hemorrhage or mortality. Device-related serious adverse events are uncommon but include access site hematoma and pseudoaneurysm, arterial perforation, and arterial dissection. Transient intraprocedural vasospasm is also uncommon but is sometimes treated (36).

3. Treatment of complications

New developments in treatment of cerebral oedema

Early discussion about care options and possible outcomes in patients with high risk of developing brain swelling

According to the AHA/ASA guidelines -2019, brain swelling can cause serious and even life-threatening complications in patients with large territorial cerebral and cerebellar infarctions. Although less severe swelling can be managed medically, surgical treatment may be the only effective option for very severe cases; in such instances, timely decompressive surgery has been shown to reduce mortality. Nevertheless, there is evidence that persistent morbidity is common, and individual preexisting decisions about end-of-life and degree of treatment performed in the face of severe neurological injury must be considered (7). Therefore, they recommend that in patients with large territorial cerebral and cerebellar infarctions who are at high risk for developing brain swelling and herniation. Discussion of care options and possible outcomes should take place quickly with patients (if possible) and family or next of kin. Medical professionals and caregivers should ascertain and include patient-centered preferences in shared decision- making, especially during prognosis formation and when considering interventions or limitations in care (7).

Brief moderate hyperventilation is a reasonable treatment for patients with brain swelling

Use of brief moderate hyperventilation (Pco2 target, 30–34 mm Hg) is a reasonable treatment for patients with acute severe neurological decline from brain swelling as a bridge to more definitive therapy (7). This conclusion is based on data on the use of hyperventilation for the management of increased intracranial pressure from patients with traumatic brain injury show a rapid reduction in intracranial pressure with return toward baseline over the next few hours (7).

Decompressive craniectomy in patients ≤60 years old gave better outcome than in patients >60 years old.

The pooled results of RCTs demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction in patients <60 years of age, with an absolute risk reduction in mortality of 50% at 12 months. These findings were noted despite differences in the clinical trials in terms of inclusion and exclusion criteria, percent of MCA territory involved, and surgical timing. There is evidence that patients >60 years of age can have a reduction in mortality of ≈50% when decompressive craniectomy for malignant MCA infarction is performed within 48 hours of stroke onset. However, functional outcomes in elderly patients seem to be worse than those in patients <60 years of age (38).

The AHA/ASA guidelines-2019 recommend that in patients ≤60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion is reasonable. In patients >60 years with same, decompressive craniectomy with dural expansion may be considered (7).

General view about cerebral oedema

Cerebral oedema also called brain swelling is the most serious complication of ischemic stroke which can happen with a rapid and fulminant course over 24 to 36 hours from stroke onset but can also follow a more gradual course over several days to week. Cerebral oedema leads to neurologic deterioration which typically includes decreased arousal, pupillary changes, and worsening of motor responses. Malignant edema after ischemic stroke is associated with younger age, higher NIHSS scores on admission, and parenchymal hypoattenuation of more than 50 percent of the MCA territory on initial head CT or MR. Risk of massive edema is particularly high in patients with DWI lesions >145 cm^3. Additional CT findings that may be predictive of malignant edema include midline shift of the septum pellucidum >5 mm, infarction of additional vascular territories and a low ASPECTS score. Revascularization within 24 hours after stroke onset was associated with a reduced risk of malignant edema (39).

Treatment of cerebral oedema includes surgical hemicraniectomy and intensive supportive care like intubation and mechanical ventilation if needed, elevation of the head of the bed, osmotic therapy (mannitol or hypertonic saline), and brief periods of hyperventilation as needed, control of blood pressure, blood glucose, temperature, and prevention of other secondary complications such as aspiration and deep venous thrombosis (39).

Decompressive hemicraniectomy (DHC) with durotomy is a surgical technique which involves removal of bone tissue (skull) and incision of the restrictive dura mater covering the brain, allowing swollen brain tissue to herniate upwards through the surgical defect rather than downwards to compress the brainstem. DHC relieves the increased intracranial pressure and brain tissue shifts, prevents further brain injury, and improves cerebral perfusion pressure (39). Hemicraniectomy is proven to reduce mortality, but most surviving patients are left with

major disability. Thus, the dilemma for patients and families is that surgery may leave patients alive with severe disability, while medical management alone most often results in death (39).
Given the dire prognosis for survival associated with medical treatment, UpToDate suggests decompressive hemicraniectomy within 48 hours of stroke onset for patients age ≤60 years with an indisputable diagnosis of malignant hemispheric infarction (with >50 percent infarction of middle cerebral artery [MCA] territory by head computed tomography [CT] or magnetic resonance imaging [MRI]) who are at high risk of developing malignant edema and who value survival despite the substantial likelihood of survival with severe disability. This surgery may also be offered on a case-by-case basis for otherwise healthy patients older than 60 years of age and beyond 48 hours after stroke onset (39).

New developments in prevention/treatment of dysphagia and pneumonia

Dysphagia screening test in all ischemic stroke patients

The AHA/ASA guidelines -2019 recommend dysphagia screening before the patient begins eating, drinking, or receiving oral medications even though there were insufficient data to determine whether implementation of a dysphagia screening protocol reduces the risk of death or dependency. Early dysphagia screening can be effective to identify patients at higher risk for aspiration, which is associated with greater risk of pneumonia, even if dysphagia screening was not associated with reduced rates of pneumonia or improvements in death or disability when tested in RCTs (7).

Oral hygiene protocols to reduce the risk of pneumonia after stroke

Limited studies suggest that intensive oral hygiene protocols might reduce the risk of aspiration pneumonia in patients with acute stroke. Sørensen et al showed that intervention with standardized dysphagia screening and diet and standardized oral hygiene with antibacterial mouth rinse with chlorhexidine reduced pneumonia (7% versus 28%) compared with a historical control group in which patients were unsystematically screened for dysphagia within 24 hours and received unsystematic and arbitrary oral hygiene without chlorhexidine (40). A Cochrane review that included 3 studies found that oral care and decontamination gel versus oral care and placebo gel reduced the incidence of pneumonia in the intervention group (41). Wagner et al conducted a cohort study comparing rates of pneumonia in hospitalized stroke patients before and after implementation of systematic oral hygiene care. The unadjusted incidence of hospital-acquired pneumonia was lower in the group assigned to oral hygiene care compared with control subjects (14% versus 10.33%). After adjustment for confounders, the OR of hospital-acquired pneumonia in the intervention group remained significantly lower at 0.71 (42).

Enteral diet within 7 days of administration gave advantage

Enteral diet should be started within 7 days of admission after an acute stroke. For patients with dysphagia, it is reasonable to initially use nasogastric tubes for feeding in the early phase of stroke (starting within the first 7 days) and to place percutaneous gastrostomy tubes in patients with longer anticipated persistent inability to swallow safely (>2–3 weeks) (7,43). The FOOD RCTs (Feed or Ordinary Diet; phases I–III), completed in 131 hospitals in 18 countries, showed that supplemented diet was associated with an absolute reduction in risk of death of 0.7% and that early tube feeding (within 7 days of admission) was associated with an absolute reduction in risk of death of 5.8% and a reduction in death or poor outcomes of 1.2% (44).

Overview about dysphagia

Dysphagia related to stroke is called oropharyngeal dysphagia which is swallowing impairment of the upper digestive tract including delays in the timing of movements, reduced range of movements, and frank aspiration. Dysphagia is a common complication of stroke and is a major risk factor for developing aspiration pneumonia (43).

Independent predictors of dysphagia on initial presentation include male gender, age greater than 70, disabling stroke, impaired pharyngeal response, incomplete oral clearance, and palatal weakness or asymmetry (43). About 90% of patients will improve spontaneously to a safe swallowing function by two weeks, while other minority of patients have persistent dysphagia (43).

It is important to screen patient for dysphagia before administering any oral medications or food to prevent aspiration (6,7,43). The simplest test is the water swallow test which is done when the patient is awake and alert. The patient is positioned upright in bed as high as tolerated between 30 to 90 degrees and instructed to drink 90 ml of water from a cup by mouth (use of a straw is permitted) slowly and steadily without stopping. The test is passed if the patient is able to drink the entire volume of water without coughing or choking during or immediately (eg, within one minute) after swallowing. Another test is video fluoroscopy with modified barium swallow can be performed once the patient is stable to assess the severity of oropharyngeal dysfunction and risk of aspiration (43).

Supportive treatment for ischemic stroke patients with dysphagia is nil per os (NPO) initially (6,7,43). Intravenous hydration with normal saline should be administered to maintain volume status. In patients who have persistent dysphagia, or who cannot take food or fluid orally due to altered mental status, and/or mechanical ventilation should receive nutrition and hydration via nasogastric, nasoduodenal, or percutaneous endoscopic gastrostomy tubes (43).

The new developments in prevention/treatment of DVT

Intermittent pneumatic compression (IPC) is useful to prevent DVT

In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended by the AHA/ASA guidelines-2019 over routine care to reduce the risk of deep vein thrombosis (DVT) (7). CLOTS 3 (Clots in Legs or stockings After Stroke) was a multicenter trial enrolling 2867 patients in 94 centers in the United Kingdom and comparing the use of IPC with routine care and no IPC with routine care in immobile stroke patients for venous thromboembolism prophylaxis (45). The primary outcome of DVT occurred in 122 of 1267 participants with IPC (9.6%) compared with 174 of 1245 participants without IPC (14.0%). Among patients treated with IPC, there was a statistically significant improvement in survival to 6 months, but no improvement in disability. Contraindications to IPC include leg conditions such as dermatitis, gangrene, severe edema, venous stasis, severe peripheral vascular disease, postoperative vein ligation, or grafting, as well as existing swelling or other signs of an existing DVT (7,45).

Overview about deep venous thrombosis

Deep venous thrombosis (DVT) is a serious complication of stroke because it may lead to life-threatening pulmonary embolism. The prevalence of DVT after acute stroke arranges between 1 to 10 percent. DVT development may occur as early as the second day after stroke onset and has a peak incidence between two to seven days. Patients with hemiparesis, immobility, severe stroke, and advanced age are at high risk of developing deep vein thrombosis (46).

Deep venous thrombosis prophylaxis is indicated for all ischemic stroke patients. UpToDate suggests a combination of thigh-length intermittent pneumatic compression (IPC) and low molecular weight (LMW) heparin in patients who have no contraindications and should be started at admission. For patients treated with intravenous thrombolysis, IPC should be started on admission and pharmacologic DVT prophylaxis should be delayed until 24 hours after intravenous thrombolysis. Additional pharmacologic DVT prophylaxis is not needed for patients receiving full-dose heparin or oral anticoagulation for another indication (46). Using graduated compression stockings for DVT prophylaxis in acute stroke is not recommended (6,7,46).

Deep vein thrombosis should be suspected in patients who present with leg swelling, pain, warmth, and erythema. Symptoms are usually unilateral but can be bilateral. Symptoms are confined to the calf in patients with isolated distal DVT, while patients with proximal DVT may have calf or whole leg symptoms. Pulmonary embolism has a wide variety of presenting features, ranging from no symptoms to shock or sudden death. The most common presenting symptom is dyspnea followed by chest pain and cough. However, many patients, including some with large pulmonary emboli, have mild or nonspecific symptoms or are asymptomatic (46).

For patients with acute proximal DVT, symptomatic distal DVT, or hemodynamically stable patients with pulmonary embolism, an inferior vena cava filter should be placed promptly if the bleeding risk associated with full-dose anticoagulant therapy is excessive. Full-dose anticoagulation may be appropriate for patients with acute ischemic stroke who have small to moderate sized infarcts, but is generally avoided for the first one to two weeks after stroke onset for patients with large infarcts. For patients with severe acute pulmonary embolism who have contraindications to anticoagulation and thrombolysis, catheter or surgical embolectomy can be used if the necessary resources and expertise are available (46).

4. Secondary prophylaxis

Without secondary prophylaxis 30% of ischemic stroke patients will have recurrent stroke during the first 5 years after the first stroke event. Good secondary can reduce 80% of these patients (47). Secondary prophylaxis includes antithrombotic therapy and reducing modifiable risk factors such as, hypertension, dyslipidemia, diabetes, smoking, and physical inactivity (1,6,7,47).

The new developments in secondary prophylaxis

Dual antiplatelet therapy is effective as secondary prophylaxis in minor ischemic stroke patients

Dual antiplatelet therapy (ASA plus clopidogrel) is strongly recommended by the AHA/ASA guidelines-2019 as secondary prophylaxis in patients with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase. The therapy should be started within 24 hours from symptom onset and continued for 21 days (7). This statement was based on the CHANCE (48) and the POINT trials (49). However, the effectiveness is only for 90 days from symptom onset (7).

Ticagrelor is not recommended over aspirin in minor ischemic stroke patients

The recently completed SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA. With a primary outcome of time to the composite end point of stroke, MI, or death up to 90 days, ticagrelor was not found to be superior to aspirin (50). However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin (7).

Abciximab is harmful for acute ischemic stroke patients

The administration of the IV glycoprotein IIb/IIIa inhibitor abciximab as medical treatment for AIS is potentially harmful and should not be performed (7).

A recent Cochrane review of IV glycoprotein IIb/IIIa receptor antagonists in the treatment of AIS found that these agents are associated with a significant risk of ICH without a measurable improvement in death or disability (51).

The majority of trial data apply to abciximab, which was studied in the AbESTT trial (A Study of Effectiveness and Safety of Abciximab in Patients With Acute Ischemic Stroke) (52). The phase III trial was terminated early because of an unfavorable risk-benefit analysis (7).

Overview about antithrombotic therapy

Antiplatelet therapy: - Antiplatelet therapy includes mono therapy (ASA or clopidogrel) and combination therapy (ASA plus clopidogrel, ASA plus dipyridamole or ASA plus clopidogrel plus dipyridamole).

Generally, administration of ASA is recommended in all ischemic stroke patient within 24 to 48 hours after symptom onset. For ischemic stroke patient who were treated with IV alteplase, administration of ASA is often started 24 hours later. Aspirin should not be administered as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy (6,7,53).

When the cause of ischemic stroke is determined, antiplatelet therapy is recommended mainly in noncardioembolic stroke. Clopidogrel or combination of ASA and dipyridamole is recommended in preference to mono ASA therapy (5,7,47).

For patients presenting with minor noncardioembolic ischemic stroke (NIHSS score $\leq$3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset (7).

Noncardioembolic ischemic stroke patient with heart failure should be treated with clopidogrel or ASA plus dipyridamole (not anticoagulant) unless there are other factors such as serious dyskinesia of the heart, thrombosis in the left ventricle or new brain infarction under antiplatelet therapy (6).

Ischemic stroke patients with: PTO, biologic valve, problem with aorta valve or mitral valve, and without AF, it is recommended to use clopidogrel or combination of ASA and dipyridamole in preference to anticoagulation (6).

For patients who have a noncardioembolic AIS while taking aspirin, increasing the dose of aspirin or switching to an alternative antiplatelet agent for additional benefit in secondary stroke prevention is not well established. For patients who have a noncardioembolic AIS while taking antiplatelet therapy, switching to warfarin is not indicated for secondary stroke prevention. In patients with noncardioembolic ischemic stroke, treatment with triple antiplatelet therapy (aspirin+clopidogrel+dipyridamole) for secondary stroke prevention is harmful and should not be administered (7).

The selection of an antiplatelet agent should be individualized based on patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (53).

Anticoagulation therapy: - Anticoagulation therapy includes mono therapy (warfarin, heparin, direct oral anticoagulation/DOAC) and combination therapy (warfarin plus DOAC).

Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke, depending on the abnormality and the

clinical circumstances. However, this therapy is recommended mainly for cardioembolic stroke patients (6,7,53).
For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation (in preference to warfarin) between 4 and 14 days after the onset of neurological symptoms (6) . However, patients with mechanical heart valve must have warfarin (not DOAC) (1,6).

Combination of antiplatelet and anticoagulant:

For patients with a history of ischemic stroke, atrial fibrillation, and coronary artery disease, the usefulness of adding antiplatelet therapy to oral anticoagulants is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events.
If a patient with mechanical heart valve develops brain infarct while INR is normal should have ASA in addition to warfarin (6).
Ischemic stroke patients who also have heart infarction should receive anticoagulation (low molecular heparin /LMH) plus antiplatelet therapy (ASA/ clopidogrel) at least 3 months (6).

Overview about modifiable risk factors

Hypertension

Ischemic stroke patients who have a blood pressure above goal are recommended to have antihypertensive therapy. Goal of blood pressure for those who have other risk factors such as cardiovascular disease, heart failure, diabetes mellitus, chronic kidney disease is <130/80 mmHg, and <140/90 mmHg for those who do not have any risk factors (6,47).
The choice of drug is similar as in other hypertensive patients. Monotherapy is recommended when blood pressure <20/10 mmHg above goal. ACE inhibitors, ARBs, calcium channel blockers and diuretic are all reasonable choice. However, betablocker is not recommended (47).

Dyslipidaemia

Medicines for lipid-lowering therapy includes statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Among these three, statins are the best studied and have proven efficacy for reducing the risk of recurrent ischemic stroke (47).
According to the guideline from AHA/ASA, patients already taking statins at the time of onset of ischemic stroke should continue statin therapy during the acute period and for those who qualify for statin treatment, in-hospital initiation of statin therapy is reasonable (7).
Generally, a high-intensity statin therapy is recommended independent of the baseline LDL-C, to reduce the risk of stroke and cardiovascular events (7,47). UpToDate recommends using atorvastatin 80 mg/day, since this was the agent and dose used in the SPARCL trial that showed a benefit for secondary ischemic stroke prevention (47).
The goal of statin therapy is to reduce LDL-C level by 50% or achieve LDL-C <70 mg/dL (1.8 mmol/L) in ischemic stroke patients with cardiovascular disease who tolerate high-intensity statin therapy (7,47). For patients who are intolerant of high-intensity statin therapy, the maximally tolerated dose of a statin should be used; alternatives are moderate-intensity statin therapy or low-intensity statin therapy (7,47).
For patients whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) despite maximally tolerated statin therapy, adding ezetimibe or a PCSK9 inhibitor is reasonable (7,47).

Diabetes

Patients with diabetes mellitus have approximately twice the risk of ischemic stroke compared with those without diabetes. In addition, the risk of stroke associated with diabetes is higher in women than in men (47).
There is evidence that tight glucose control reduces microvascular complications. However, there is no proven benefit of intensive glucose-lowering therapy for reducing macrovascular outcomes, such as stroke and death in patients with type 2 diabetes (47).

The AHA/ASA guideline recommends diabetes screening in all ischemic stroke patients. It is more accurate to use haemoglobin A_{1c} than fasting plasma glucose and oral glucose tolerance test in the immediate postevent period (7).
For most patients with diabetes, a reasonable goal of therapy is a glycated hemoglobin (A_{1c}) value of ≤7 percent. Diet, exercise, oral hypoglycemic drugs, and insulin are proven methods to achieve glycemic control (47).

Smoking

Cigarette smoking is associated with an increased risk for all stroke subtypes and has a strong, dose-response relationship for both ischemic stroke and subarachnoid hemorrhage. Evaluation of former smokers found that the excess risk disappeared within two to four years after the cessation of smoking (47).
In the Nurses' Health Study, smokers had a relative risk of stroke of 2.58 compared with never smokers. In the Framingham Heart Study, the odds ratio for moderate carotid stenosis was 1.08 for each five pack-years of smoking. Among 10,938 normotensive subjects in a prospective Swedish cohort study, about 39 percent of strokes were attributable to smoking .
There are no randomized controlled trials of smoking cessation compared with no intervention for stroke prevention. However, observational studies have shown that the elevated risk of stroke due to smoking declines after quitting and is eliminated by five years later (47).
The (AHA/ASA) guidelines recommend smoking cessation for patients with stroke or transient ischemic attack (TIA) who smoke tobacco, counseling with or without pharmacologic therapy to assist in quitting, and avoidance of environmental tobacco smoke (7).

Physical inactivity

Patients with ischemic stroke or TIA who are capable of regular exercise should engage in moderate-intensity physical exercise performed for a minimum of 10 minutes four times a week or vigorous-intensity exercise performed for a minimum of 20 minutes twice a week. Moderate-intensity exercise is defined as activity sufficient to break a sweat or noticeably raise the heart rate like walking briskly, using an exercise bicycle (47).
Increasing evidence suggests that low physical activity and prolonged sitting increases the risk of cardiovascular disease, including stroke. Additional support that physical inactivity is a risk factor for stroke comes from studies showing the benefit of increased physical activity and exercise for reducing the risk of cardiovascular events (47).

Discussion

Will Tenecteplase replace alteplase?

As mentioned previously in the thesis, while the Norwegian guidelines still recommend using IV alteplase as the only thrombolytic medication in treatment of acute ischemic stroke, the AHA/ASA guidelines recommend using tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) in ischemic stroke patients prior to thrombectomy and tenecteplase administered as a 0.4-mg/kg single IV as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.
Until now, there are at least five different RCTs which compared the efficacy of tenecteplase with alteplase (26, 54-57). These trials have demonstrated that tenecteplase is noninferior or somewhat more effective than alteplase in treatment of ischemic stroke.
The first trial was prematurely terminated after only 112 suspected acute ischemic stroke patients within 3 hours had been randomized to tenecteplase 0.1 milligrams per kilogram (mg/kg), tenecteplase 0.25 mg/kg, tenecteplase 0.4 mg/kg, or standard dose alteplase (0.9 mg/kg) (54). Group of patients who received tenecteplase at 0.4 mg/kg had lowest rate of

neurological outcomes at three months (measured as mRS 0 to 1) and highest rate of symptomatic intracranial haemorrhage (54). There were no statistically significant differences among the other groups, but Zitek, et al mean that there was a trend towards higher percentages of patients having good neurologic outcomes in the tenecteplase 0.1 mg/kg and 0.25 mg/kg groups as compared to the alteplase group: tenecteplase 0.1 mg/kg 45.2%, tenecteplase 0.25 mg/kg 48.4%, and alteplase 41.9% (58).

The second trial compared three groups of ischemic stroke patients (25 patients in each group) who were received tenecteplase at 0.1 mg/kg, 0.25 mg/kg and alteplase 0.9 mg/kg (55). This trial demonstrated that the two tenecteplase groups had greater reperfusion ($P=0.004$) and clinical improvement ($P<0.001$) at 24 hours than the alteplase group and the higher dose of tenecteplase (0.25 mg per kilogram) was superior to the lower dose and to alteplase for all efficacy outcomes, including absence of serious disability at 90 days (in 72% of patients, vs. 40% with alteplase; $P=0.02$). However, enrolled patients were selected by using CT perfusion imaging which was not one of those acute neuroimaging methods recommended by any guidelines.

The third trial (56) compared tenecteplase 0.25 mg/kg to alteplase for patients with suspected acute ischemic stroke within 4.5 hours of symptom onset. A total of 104 patients were enrolled, with 52 assigned to each group. This trial also showed no significant difference between groups, but Zitek et al, once again recognized a slightly trends towards early neurologic improvement at 24 hours (40% vs 24%) and a higher percentage of good neurologic outcome at 90 days (28% vs 20%) (58).

The fourth trail compared tenecteplase 0.4 mg/kg and standard dose alteplase for patients with suspected acute ischemic stroke with 4.5 hours or less. A total of 549 patients were randomized to the tenecteplase group and 551 were randomized to the alteplase group. This trial found no difference between groups in the primary outcome of good neurologic outcome at 90 days (64% tenecteplase vs 63% alteplase) (57).

The fifth trial compared tenecteplase 0.25 mg/kg to standard dose alteplase for patients with symptoms of acute ischemic stroke for less than 4.5 hours prior to thrombectomy. There were 101 patients in each group. This trial showed a statistically significant difference between groups with regards to the primary outcome of reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment (22% in the tenecteplase group,10% in the alteplase group). Patients in the tenecteplase also had superior functional neurologic outcomes at 90 days as compared to the alteplase group (26). This trial formed the basis for the AHA/ASA recommendation of using Tenecteplase instead of alteplase in ischemic stroke patients prior to thrombectomy.

There are four meta-analyses which used the trials described above. Two of these reported significant improved early neurological improvement with tenecteplase. One reported significantly greater complete recanalization in patients treated with tenecteplase. However, all these meta-analyses reported no differences with regards to neurologic recovery and mortality between tenecteplase and alteplase (58).

Alteplase is still the only thrombolytic medication improved by the Food and Drug Administration for treatment of acute ischemic stroke. While the most trials failed to demonstrate a significant benefit of using tenecteplase compared to alteplase, many people are optimistic about using tenecteplase because of the advantage in administration (a single bolus of tenecteplase in contrast to a bolus followed by 1-hour infusion of alteplase). In addition, there is evidence that tenecteplase costs much less than alteplase which can make tenecteplase more favourable than alteplase (58).

How to avoid stroke mimics?

Stroke mimic remains as a major diagnostic challenge for physician in acute diagnostic of ischemic stroke. As mentioned previously in the thesis, suspected ischemic stroke patients need only NCCT or MRI before administration of IV alteplase. These neuroimaging methods can detect some stroke mimics such as brain tumours, abscess, but not all. In addition, physicians normally have limited time for history and clinical evaluation in suspected ischemic stroke patients before decision-making of thrombolysis. This leads to many stroke mimic patients were treated with IV alteplase. Little is known about whether NIHSS could help to differentiate between ischemic stroke and stroke mimic in patients being evaluated for intravenous thrombolysis. A cross sectional-study (59) found that about 15% of suspected ischemic stroke patients has stroke mimic. There was a significant correlation between age and early diagnosis of stroke or stroke mimic where the patients with stroke mimic are often younger (median age is 67) than patients with real ischemic stroke (mean median age is 72). This study also found that the highest frequency of stroke mimics was related to brain tumours (10,5%), hypoglycaemia (9.2%) and toxic poisoning (8,5%). If this study is reliable, it would be easy to exclude stroke mimic by CT or MRI neuroimaging to detect brain tumours. Quick test for blood glucose is also very simple to do and recommended by all guidelines before any specific treatments of ischemic stroke.

In another retrospective study more than 50% of stroke mimic was accounted for by epilepsy, psychiatric disorder, and hypoglycaemia. The study suggested therefore familiarizing with the clinical features of these diseases is necessary to differentiate it from stroke. For example, patients with epilepsy/seizures or migraine often have some prodromal event or aura, which can tip off clinicians. The study also found that other factors which can be helpful in distinguish mimic stroke from real stroke are systolic blood pressure ≤140 mmHg, NIHSS ≤5, a history of diabetes mellitus and no history of arrhythmia (60).

Another study which collected stroke/MRI data bank from 2004 to 2010 with 648 suspected ischemic stroke patients treated with rt-PA. Only 42 of 648 (6,5%) had final diagnosis as stroke mimic, and 50 % of stroke mimics is seizures (61). This study concluded that patients with stroke mimic had less often typical stroke symptoms like dysphasia, facial palsy, hemiparesis, horizontal gaze palsy and visuospatial neglect, while aphasia and accompanying convulsions occurred more often.

Is MRI to detect DWI-FLAIR mismatch a good solution for Wake-Up stroke patients?

Wake-up stroke is when a patient awakens with stroke symptoms that were not present prior to falling asleep. This happens in 1 of every 5 ischemic stroke patients. Normally, these patients will be excluded for thrombolysis and thrombectomy but the AHA/ASA guidelines-2019 and the Norwegian guidelines recommend using DWI-FLAIR mismatch to select eligible patients for thrombolysis when the time from symptom onset is unclear. However, many people still express concern about application of this method in practice. Rønning claimed that it is still open to question whether wake-up stroke patients can have thrombolysis based on a normal standard CT, or whether they ought first to be treated after scans that show DWI-FLAIR mismatch and/or core/penumbra mismatch. As a means of distinguishing between infarctions with symptom onset before and after 4.5 hours, DWI-FLAIR mismatch has proven to be of uncertain sensitivity and specificity. There are also quite large individual differences in the conclusions drawn from the findings. It is conceivable that selection based on mismatch studies entails a risk of patients who wake up with stroke symptoms, and who should have received thrombolysis, not receiving it because of overly stringent image selection criteria. The importance of scans therefore remains unclarified (62).

In practice, MRI is not as widely available as CT as mentioned earlier in this thesis. If we send ischemic stroke patients to another hospital where MRI is available would take more time and can result in that the patient is no longer eligible for thrombolysis treatment by the time MRI is done. Nevertheless, for hospital/stroke centres where MRI to detect DWI-FLAIR mismatch is possible. Barton reported successful implementation of a protocol similar to the WAKE-UP trial in a community hospital setting that uses DWI/FLAIR mismatch to possibly treat patients that awaken with stroke symptoms (61).

How can we define a mild disabling stroke?

According to the AHA/ASA guidelines-2019, thrombolysis should be administered in mild but disabling ischemic stroke patients while mild nondisabling stroke patients should not receive IV alteplase. How can we determine a mild stroke is disabling or not?

According to Fischer et al (63) mild and disabling stroke is the same as minor stroke. However, a consensus definition of minor stroke is lacking. They tested 6 minor stroke definitions as following:

A: Patients with NIHSS score ≤1 and normal consciousness.

B: Patients with lacunar-like syndrome

C: Patients with motor deficits with/or without sensory deficits

D: Patients with NIHSS score ≤ 9 (excluding those with aphasia, neglect, or decreased consciousness)

E: Patients with NIHSS score ≤9

F: Patients with NIHSS score ≤3

They concluded that A and F are two most suitable definitions of minor stroke. Both definitions are however based only on NIHSS score which also has some limitations as discussed somewhere in this thesis. In addition, none of these definitions can exclude transient ischemic attach/TIA. Therefore, a clearer guideline for evaluating patients with mild stroke symptoms should be established, and more studies should be conducted in this field.

Blood pressure control in AIS needs a more complex rapprochement?

Abrupt BP rise is a common phenomenon in acute ischemic stroke. It is observed in approximately 75% of patients while a minority of ischemic stroke patients had low or fluctuated BP during acute phase. Abrupt BP rise is also called acute hypertensive response (AHR) because it normally reflects a transient response where BP reaches its highest value during the first hours after stroke onset, then gradually declines and settles within the first 7 to 10 days after stroke onset (66).

What causes AHR is still unknown, but some believe that AHR may be related to pre-existing conditions such as inadequate treated or undiagnosed hypertension, diabetes. It may also be caused by stroke-related damaging of the brain regions which involve autonomic regulation or activation of sympathetic adrenomedullary pathway or others stroke consequences like urine retention, infection, cerebral oedema, headache or even stress due to hospitalization (67).

The relationship between BP and clinical outcome in AIS has been investigated in many studies. Most of them found that extreme high or low blood pressure and high BP variability have been related to worse outcome. However, optimal BP for ischemic stroke patients remains unknown (7).

According to the AHA/ASA guidelines-2019, hypotension and hypovolemia should be corrected to maintain a systemic perfusion level necessary to support organ function. The guidelines however do not indicate the BP level below which the treatment should be initiated, and which BP should be a treatment goal (7).

Still according to the AHA/ASA, eligible patients for thrombolysis should have their blood pressure lower than 185/110 mmHg before IV alteplase administration and less than 180/105 mmHg 24 hours after thrombolysis (7). However, BP levels higher than those recommended are observed in up to 50% of patients who are eligible for intravenous thrombolysis (68). It has been demonstrated that high BP significantly increased the risk of haemorrhagic transformation. Patients with BP > 170 mmHg have four times risk of haemorrhagic transformation compared to those with BP at 141-150 mmHg (24). However, in ischemic stroke patients treated intensively to achieve BP goal 130-140mmHg, the outcome was not better than group treated according to the guidelines above (69).
Cerebral blood flow within the penumbra is highly dependent on individual cerebral vascular anatomy (collateral blood flow) and in the case of dysregulated cerebral autoregulation it follows systemic blood pressure (1).
Many studies found that high BP in acute phase is associated with better collaterals while others demonstrate that lower BP may favour better pial collateral recruitment.
Similarly, optimal BP values for ischemic stroke patients who are eligible for thrombectomy are also still debatable.
In a review study Gasecki et al claimed that in contrast to BP values, the history of hypertension and related end organ damage may serve as a reliable predictor of stroke outcome and a paradigm shift in the management of BP in AIS is needed: from simplistic, based just on sole BP values, to more complex, including the identification and management of compensatory mechanisms, modified by chronic disease (especially hypertension), adjusted to local hemodynamic and metabolic demands in the ischemic area (69).

Summary

In this thesis have we focused on the new developments in treatment of ischemic stroke, in addition to supplying medical students with overview about recurrent treatment and prophylaxis. The most important new developments are:
NCCT in acute phase is adequate for diagnostic and selecting eligible patients for thrombolysis.
People who are suspected to have ischemic stroke should be examined with NNCT and receive iv thrombolysis. CTA/or MRI is done after NCCT to select patients who can be treated with mechanical thrombectomy.
Wake-up stroke patient can still be treated with thrombolysis if they have DWI-FLAIR mismatch and DWI lesion is less than one third of the territory of the MCA.
Tenecteplase is an alternative for IV alteplase in patients who also receive thrombectomy.
Stroke patients within 6 and 24 hours from symptom onset can still be treated with thrombectomy if they meet DAWN or DEFUSE 3 criteria.
Brief moderate hyperventilation is useful in treatment of brain swelling. However, early discussion with patients and family about possible outcome is necessary in patients who are at high risk of developing brain swelling.
Dysphagia screening test in all ischemic stroke patients before oral medications and diet is simple and important to identify patients who have dysphagia and prevent aspiration and pneumonia. Intermittent pneumatic compression (IPC) is useful in prevent DVT and pulmonary thrombosis.
Dual antiplatelet therapy is effective as secondary prophylaxis in minor ischemic stroke patients, but the effectiveness last for 90 days after symptom onset.
Recurrent stroke can be significant reduced if the patient has good control of blood pressure, lipid profile, blood glucose, quit smoking and do regular exercise. Antithrombotic therapy is indicated in all ischemic stroke patients which includes mainly of antiplatelet (ASA, clopidogrel) for patients with noncardioembolic ischemic stroke and anticoagulation (warfarin, heparin, DOAC) for patients with cardioembolic ischemic stroke.

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