Supplemental Material

Chinese Stroke Association Guidelines for Clinical Management of Cerebrovascular Disorders

Executive Summary and 2019 Update of Clinical Management of Ischemic Cerebrovascular Diseases

Section 1 Definitions associated with ischemic cerebrovascular diseases.

The definitions of ischemic cerebrovascular disease are shown in Table 1.

Section 2 Emergency assessment and diagnosis of ischemic stroke patients

Please refer to Figure 1 for details of the management process for ischemic stroke patients in the acute phase.

I. First assessment of emergency

(I) Medical history collection

Acute ischemic stroke (AIS) patients suffer from acute onset. It is very important to inquire about the time of occurrence of symptoms, onset characteristics and progress, including symptom persistence, fluctuations and relief. If the disease starts onset during sleep, the time when the patient's last normal performance should be recorded. These patients may also get sick shortly before waking up, and the onset time is uncertain, but clinically the final normal time should still be calculated as the last normal time [1-2]. Using MRI to screen wake-up stroke patients who are not suitable for thrombectomy, intravenous thrombolysis helps patients get good prognosis [3]. Before the occurrence of current symptoms, some patients will have similar TIA symptoms that can be relieved automatically. The time window for thrombolytic therapy is calculated based on the occurrence time of current symptoms. The inquiry about whether there are causes related to haemorrhagic stroke before the occurrence of symptoms, such as emotional excitement, intense exercise, sudden change of body position, excessive blood pressure reduction, as well as whether there is a history of

stroke or similar stroke-like diseases (such as epilepsy and hypoglycaemia attacks), has certain significance for diagnosis. Other medical history should include the presence or absence of atherosclerosis risk factors (such as hypertension, diabetes, and hyperlipidaemia) and heart disease risk factors (such as atrial fibrillation), drug abuse, migraine, infection, trauma, surgery and pregnancy history, and attention should be paid to the patient's recent medication, especially the presence or absence of anticoagulant drugs. For patients with consciousness disorder, doctors can ask their family members or witnesses about the disease.

(II) Physical examination

After emergency doctors and stroke team doctors evaluate the airway and respiratory and circulatory functions individually or jointly, they will immediately carry out general physical examination, including auscultation of large cervical vessels and heart.

(III) Auxiliary examination (such as blood glucose, electrocardiogram, troponin, chest radiography)

Timely imaging examination is very important for quick assessment and diagnosis of patients with possible ischemic stroke. All patients should first select urgent cranial CT examination to exclude cerebral haemorrhage, and MRI may be chosen if conditions permit, but should not delay thrombolysis therapy. For patients suspected of macrovascular occlusion, MRA or CTA should be performed as soon as possible (at the same time of thrombolysis) to determine whether intravascular treatment

conditions are available. For the process of skull imagological examination for patients suspected of ischemic stroke after entering the emergency department, see Supplemental Table 1.

For all suspected stroke patients, routine laboratory examination should be carried out immediately upon arrival at the emergency department, including blood glucose, renal function, electrolyte, blood routine including platelet count, coagulation function including international standardized ratio (INR), myocardial ischemia markers, and bedside electrocardiogram examination should be performed. Because time is of the utmost importance, thrombolytic therapy should not be delayed due to waiting for the above laboratory results, unless the patient has oral anticoagulants or obvious history of coagulation. Retrospective analysis of patients receiving intravenous thrombolysis has found that the probability of unexpected coagulation disorders and thrombocytopenia is very low [4-5].For the vast majority of patients, blood glucose test results must be acquired before thrombolytic therapy [6].

Some laboratory tests can be selected for specific patients, toxicological screening can be performed for suspected drug abuse, chest radiography can be performed for suspected aortic dissection, electroencephalogram can be performed for suspected epilepsy, lumbar puncture can be performed for suspected intracranial infection or subarachnoid haemorrhage, blood gas examination can be performed for hypoxia, and pregnancy tests can be performed for women of childbearing age.

For intravenous thrombolysis or mechanical thrombectomy, the earlier treatment is

started, the greater the benefit. Many studies abroad suggest that the average or median door-to-imaging time under different hospital configurations is less than 20min [7-10].However, a large-scale registration study in China in 2011 showed that the average door-to-needle time (DNT) in China was 116min, and the average imaging-to-needle time (INT) was 90min. Therefore, based on China's national conditions and actual clinical practice, skull imagological examination should be completed within 30min for patients suspected of ischemic stroke [11].

Recommendations

[1] It is recommended that patients suspected of having an ischemic stroke should complete finish brain imaging within 30 minutes of arrival at the emergency department (Class I, Level of Evidence B).

[2] Emergency assessment of blood glucose, renal function, electrolytes, complete blood count (including platelet count), blood coagulation (including INR), cardiac injury markers, and a bedside 12-lead ECG is recommended, but should not delay the initiation of IV rt-PA. For most patients, only the assessment of blood glucose must precede the initiation of IV rt-PA (Class I, Level of Evidence B).

(IV) Definitions of penumbra

The hypoperfusion brain tissue is divided into three parts according to function and prognosis. The centre is the irreversible infarction core, and the outermost periphery is the hypoperfusion area with intact function. The area between them is the ischemic penumbra. The brain tissue in the penumbra is at risk of irreversible ischemic damage, but this part of brain tissue can be saved if blood perfusion is restored in time. Therefore, ischemic penumbra is currently an important therapeutic target for AIS [12]. The early studies mainly explored the best time window to save the penumbra [13-14], but the general and narrow time window will cause many potentially beneficial patients to have poor prognosis due to failure to receive reperfusion therapy. With the development of multi-mode imaging, the penumbra can be accurately identified by judging whether the infarct core matches its peripheral hypoperfusion areas, which prolongs the treatment time window and has important clinical guiding value. Researchers further set a target mismatch (TMM) by comparing the relationship between different mismatch degrees and prognosis, which means that more ischemic penumbra can be saved under a specific mismatch threshold and the prognosis is better after reperfusion therapy [15]. Common imaging strategies include diffusion-perfusion imaging mismatch, CTP, clinical imaging mismatch and diffusion-flair mismatch. Other technologies such as DWI-SWI mismatch, ASL-PWI mismatch, APTW and MR OMI have been reported, but have not been applied to large-scale clinical trials [16-19].

In many large-scale clinical studies, for intravenous thrombolysis or intravascular therapy, such as DEFUSE, DEFUSE2, EPITHET, DEDAS, DAWN, and DEFUSE3, the most widely used and mature imaging strategy is diffusion-perfusion imaging mismatch (DWI-PWI mismatch) [15, 20-22]. It uses the mismatch between DWI infarction core area and PWI hypoperfusion area to identify ischemic penumbra. At present, the generally accepted set threshold is: the area with T_{max} > 6s on PWI is set as the hypoperfusion area, the area with ADC < 600×10-6mm2/s on DWI is set as the infarction core area, and the target mismatch is defined as the area with infarction core area < 70ml, ischemic penumbra > 15ml, and the area with the ratio of total hypoperfusion area to ischemic core area being > 1.8 [15].At present, required data can be directly obtained by using software such as Rapid. Although the DWI-PWI mismatch imaging strategy can accurately identify ischemic penumbra and provide important information for clinical reperfusion therapy, it is difficult to promote it in most clinical centres due to the time-consuming and labour-intensive defects of emergency MRI.

Another commonly-used method is CTP. It has been widely used in multiple large-scale clinical trials such as ESCAPE, CRISP, SWIFT PRIME, EXTEND-IA and DEFUSE 3 [15, 23-25]. At present, the generally accepted set threshold is: the area with cerebral blood flow (CBF) of the affected side lower than 30% of normal tissue is set as the infarction core lesion, the area with T_{max} > 6s is set as the hypoperfusion area, and the definition of target mismatch is the same as before. However, setting CBF <

30% as the infarction core in this imaging strategy is not as accurate as DWI, and more research is needed to evaluate it. Considering that emergency CT is currently most widely used and the examination time is short, CTP may have better clinical operability.

The 2018 DAWN study effectively extended the time window for intravascular treatment to 24h based on DWI/CTP-clinical mismatch. The researchers divided the patients into three groups according to the size, age and NIHSS score of the imaging lesion: Group A was over 80 years old, NIHSS ≥ 10 and infarction core < 21ml. Group B was under 80 years old, NIHSS ≥ 10 and infarction core < 31ml. Group C was under 80 years old, NIHSS ≥ 20 and infarction core of 31--51ml. Finally, the clinical trial was terminated in advance due to the obvious benefits of patients in the intravascular treatment group. Therefore, the imaging strategy is promising, but it still needs to be verified by more clinical practice [26].

The DWI-FLAIR mismatch strategy is often applied to patients with wake-up stroke or unclear onset time, such as PRE-FLAIR, WAKE-UP and other studies. DWI-FLAIR mismatch is defined as lesions visible on DWI but no high signal in corresponding parts on FLAIR [27]. Researchers believe that DWI-FLAIR mismatch may indicate stroke that occurs within 4.5h hours. In the WAKE-UP study, the intravenous thrombolysis group had better clinical prognosis, but it also increased the risk of intracranial haemorrhage [28].

Supplemental Table 2 summarizes the set thresholds of different imaging strategies for ischemic penumbra. At present, some studies have pointed out that it is not accurate to determine ischemic penumbra with a specific threshold, and proposed a multi-parameter analysis model that includes imaging and clinical data, that makes use of CTP, NIHSS score and age as parameters for algorithm analysis, or selects DWI and PWI parameters, NIHSS score and age as parameters for analysis [29].A MR RESCUE study concluded through the algorithm model that patients after intravenous thrombolysis therapy, whether or not with ischemic penumbra, fail to benefit from intravascular treatment [30].

Recommendations

If feasible, patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DWI with MRI perfusion is recommended to aid in patient selection for endovascular therapy. Patient selected for endovascular therapy should be follow the same eligibility criteria of the two major RCTs (DAWN and DEFUSE 3) (Class IIa, Level of Evidence B).

1. Stroke CT and MRI PWI

(1) Previous RCT studies, including DIAS, DIAS-II, DIAS-III, DEDAS, DEFUSE, EPITHET and ITAIS-II study in China, used multi-mode images (CTP, diffusion-perfusion mismatch, angiography, etc.) to extend the time window to screen patients

who could receive intravenous thrombolysis, but most of the results were not beneficial. At present, some clinical trials (such as ECASS-IV) are being carried out to evaluate the guiding value of multi-mode imaging for the time window of intravenous thrombolysis [31-39].

(2) Six large RCTs, including MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT and THRACE, proved that patients with large artery occlusion can benefit from intravascular treatment within a time window of 6 hours [25,40-44].Although multi-mode images (including CTP or MRI) are used to establish the inclusion criteria in the four RCTs of REVASCAT, SWIFT, EXTEND-IA and SWIFT-Prime, only non-enhanced CT is used to screen patients with large artery occlusion in the THRACE and MR CLEAN studies. Therefore, it is believed that in the 6-hour time window, the use of multi-mode images to screen patients may exclude some patients with benefits, and may also delay the timing of treatment. However, multi-mode imaging can evaluate infarct focus, ischemic penumbra and collateral circulation, which helps guide further treatment. More high-quality RCTs are needed to evaluate its advantages and disadvantages in the future.

(3) In 2017, the DAWN study combined clinical the NIHSS score and CTP or DWI to indicate the infarct volume, and established the clinical-image mismatch criteria. The patients suspected of anterior circulation artery occlusion were screened in a 6-24 hour time window, and were divided into intravascular treatment group and traditional treatment control group. The 90d function evaluation of the intravascular treatment

was superior to that of the control group and had statistical significance (mRS score 0--2 , 49% vs. 13%, adjusted difference 33%, 95% *CI:* 21--44, posterior probability advantage > 0.999), so the clinical trial was terminated earlier [26].

In 2018, the DEFUSE 3 study used CTP or DWI-PWI to establish the imaging standard of infarction-ischemia hypoperfusion mismatch. Patients with suspected anterior circulation artery occlusion were screened in a 6-16 hour time window and randomly divided into an intravascular treatment group and a traditional treatment group, and the trial was terminated in advance because the prognosis of the intravascular treatment group was significantly better than that of the control group (mRS score 0-2 , 44.6% *vs*. 16.7%， *RR*=2.67, 95% *CI:* 1.60-4.48, *P*< 0.0001) [45]. The subgroup analysis using the DAWN inclusion criteria also confirmed the benefits. The above two studies confirmed that intravascular treatment can produce benefits beyond the time window of 6 hours. Therefore, patients should be screened strictly according to their inclusion criteria in clinical practice. In the future, more high-quality RCT is needed to explore indications for intravascular treatment beyond 6 hours.

(4) The ASPECTS score can be used to identify suspected patients with large artery stroke, create conditions for intravascular treatment, and can also be used to evaluate treatment prognosis, collateral circulation, etc. [46-50]. At present, the most commonly used ASPECTS score is based on CT. ASPECTS < 6 was used as the exclusion criterion in the ESCAPE and SWIFT-PRIME studies, and ASPECTS < 7 was used as

the exclusion criterion in the REVASCAT study [41, 42]. However, in the MR CLEAN study, there was no strict restriction on the ASPECTS score. The results showed that patients in groups 5--7 and 8--10 had no difference in benefits, and patients with 0--4 had no obvious benefits, but they cannot be used as exclusion criteria [51]. A 2017 retrospective study in China compared the clinical prognosis of patients with ASPECTS 5 and ASPECTS 6 of anterior circulation artery occlusion after intravascular treatment, and concluded that intravascular treatment could not achieve satisfactory efficacy for patients with ASPECTS 5 [52]. Some existing studies in China use ASPECTS ≥ 6 as the inclusion criteria [53]. In conclusion, ASPECTS ≥ 6 is currently used as one of the inclusion criteria for intravascular treatment, and more clinical studies are needed to verify the efficacy and safety of intravascular treatment in people with ASPECTS < 6. At present, ASPECTS scores based on CTP, CTA, MRI, etc. have become available one after another, and their accuracy, consistency and applicability need to be studied through more clinical trials [53-57].

(5) At present, most of the imaging studies on AIS are clinical trials based on intravenous thrombolysis or intravascular treatment, and there is no study specifically targeting imaging available. More imaging studies based on acute stroke may be needed in the future.

Recommendations

[1] It is unclear whether using multimodal imaging criteria to select ischemic

stroke patients who have unclear time of symptom onset for treatment with IV rt-PA is beneficial or not, therefore is not recommended outside a clinical trial (Class III, Level of Evidence B).

[2] If needed, multimodal imaging should be obtained as quickly as possible, to not delay administration of IV rt-PA (Class IIb, Level of Evidence B).

[3] It is unclear whether using perfusion imaging (CTP or PWI) for selecting patients for endovascular treatment < 6 hours is beneficial (Class IIb, Level of Evidence B).

[4] It is recommended for AIS patients meeting the eligibility criteria of the two major RCTs (DAWN and DEFUSE 3) within 6 to 24 hours of last known normal who have LVO in the anterior circulation to obtain CTP or DWI with MRI perfusion with subsequent endovascular therapy (Class IIa, Level of Evidence B).

[5] It is recommended that the ASCPECTS score based on head CT be considered when evaluating for endovascular treatment. However, the decision-making doctor must have received the training in the assessment of NIHSS and ASPECTS scores and been verified for consistency (Class IIa, Level of Evidence B).

(V) Stroke severity and score

Neurological examination should be brief and comprehensive, but thrombolytic

therapy should not be delayed. A stroke scale can be used. The National Institute of Health Stroke Scale (NIHSS) is currently the most commonly used scale in the world to evaluate neurological deficits of patients. It is easy and simple to operate, takes a short time, and its clinical application effect has been confirmed [58-59].

Recommendations

For patients with acute presentation of neurological dysfunction, medical history taking and physical examination must be performed rapidly. Medical history includes onset characteristics, predisposing factors, last known normal time, past medical history and current medication list. Physical examination includes vital signs and general physical examination. The use of NIHSS as a stroke severity rating scale is recommended (Class I, Level of Evidence A).

II. Emergency diagnosis and differential diagnosis

(I) Diagnostic criteria of AIS

1. In case of acute onset, the specific time of onset or the last normal time is traceable (onset during sleep).

2. Focal neurological impairment (weakness or numbness of one side of the face or limbs, language disorders, visual disorders, etc.), a few of which are full-face neurological impairment.

3. Imaging shows responsible ischemic lesions, or symptoms/signs last for more than

24 hours.

4. Non-vascular causes are excluded.

5. Cerebral haemorrhage is excluded by head CT/MRI.

(II) Differential diagnosis of stroke mimics

Some non-ischemic cerebrovascular diseases can also show AIS-like symptoms, which are commonly mental factors, epilepsy, hypoglycaemia, migraine, hypertensive encephalopathy, central nervous system infection, brain tumour, multiple sclerosis, electrolyte disturbance, drug toxicity, etc., and should be further identified based on medical history, clinical manifestations, laboratory examination and imaging characteristics.

Section III Reperfusion therapy for acute ischemic stroke

I. Patients within 4.5h hours of onset - intravenous thrombolysis treatment

A number of clinical trials have evaluated the efficacy and safety of rt-PA intravenous thrombolysis for acute cerebral infarction. The therapeutic time window of the study includes within 3 hours, 3--4.5 hours and 6 hours after onset. The NINDS trial result showed that the number of patients with complete or nearly complete neurological function recovery in 3 months in the rt-PA intravenous thrombolysis group was significantly higher than that in the placebo group within 3 hours, and the mortality of the two groups was similar [60]. The incidence of symptomatic intracranial haemorrhage was higher in the intravenous thrombolysis group than in the placebo group. The ECASS III trial showed that intravenous rt-PA was still effective 3--4.5 hours after onset [61]. The IST-3 trial indicated that the benefit of intravenous thrombolysis with rt-PA within 6 hours of onset is still unclear[62]. The following systematic review analyzed 12 rt-PA intravenous thrombolysis trial which included 7,012 patients, suggesting that rt-PA intravenous thrombolysis can increase the good clinical outcomes of patients within 6 hours of onset, and that rt-PA intravenous thrombolysis within 3 hours of onset has similar effects for patients aged above and under 80 years old [63].

For patients with slight or rapid improvement of stroke symptoms, who have received major surgery in the past 3 months and suffered from myocardial infarction recently, the risk-benefit ratio of intravenous thrombolysis still needs to be weighed and further

studied. Rt-PA intravenous or arterial thrombolysis may be unfavorable for patients taking direct thrombin inhibitors or direct factor Xa inhibitors, and therefore is not recommended, unless sensitive laboratory tests such as APTT, INR, platelet count, Ecarin Clotting Time (ECT), thrombin time (TT) or direct Xa factor activity test are normal, or these drugs have not been taken for more than 2 days (assuming normal renal function).

The use of multi-mode MRI or CT to help choose patients whose onset has exceeded 4.5 hour but still with penumbra and who can receive thrombolysis is still a research hotspot. In terms of the use of rt-PA, in addition to the risk of haemorrhage, partial obstruction of respiratory tract due to hematogenous oedema has also been reported. The flow chart of intravenous thrombolysis management for ischemic stroke patients within 4.5h hours of onset is shown in Figure 2.

(I) Indications and contraindications for intravenous thrombolysis

(Supplemental Table 3 and 4)

(II) Thrombolytic treatment

Basic vital functions (including body temperature, pulse, respiration, blood pressure and state of consciousness) should be closely monitored. Emergency, including intracranial hypertension, severe blood pressure abnormality, blood glucose abnormality, body temperature abnormality, and epilepsy must be handled promptly.

1. Breathing and oxygen inhalation

(1) Oxygen should be inhaled when necessary. Blood oxygen saturation should be maintained above 94%. Patients with severe airway dysfunction should be given airway support (tracheal intubation or incision) and assisted respiration.

(2) Patients without hypoxemia do not need regular oxygen inhalation.

2. Electrocardiogram monitoring and treatment of cardiac lesions

Electrocardiogram examination should be performed routinely within 24 hours after cerebral infarction. Depending on illness conditions, continuous ECG monitoring shall be carried out for 24 hours or more when conditions permit, so as to find paroxysmal atrial fibrillation or severe arrhythmia and other cardiac diseases early. Drugs that increase heart burden should be avoided or be used with caution.

3. Body temperature control

(1) For patients with elevated body temperature, the causes of fever should be found and handled. If there is infection, antibiotic treatment should be given.

(2) Antipyretic measures should be taken for patients with body temperature > 38℃.

4. Blood pressure control related to thrombolytic therapy

A number of clinical randomized trials show that the blood pressure of acute stroke patients should be controlled at systolic pressure < 180mmHg and diastolic pressure < 100mmHg before receiving Alteplase intravenous thrombolysis treatment, and the blood pressure of patients should be guaranteed to be < 180/100mmHg within 24 hours after thrombolytic therapy. For AIS patients considering thrombolytic therapy, special blood pressure management guidelines have been determined (Supplemental

Table 5), which include reducing blood pressure to below 185/110mmHg in a relaxing way so as to be suitable for intravenous rt-PA thrombolytic therapy. Once intravenous administration is given, blood pressure must be maintained at 180/105mmHg to limit the risk of cerebral haemorrhage. In the first 24 hours, the higher the blood pressure, the greater the risk of accompanying cerebral haemorrhage, with a linear relationship between the two. Some observational studies show that stroke patients with high blood pressure level [64-70] and high blood pressure variability [71] have higher bleeding risks after receiving Alteplase thrombolytic therapy. The exact blood pressure value that may lead to high-risk haemorrhagic transformation events after thromboembolic events is unclear. In the future RCT on intravenous thrombolysis treatment, the blood pressure level needs to be taken as the research target of concern.

Of the 6 clinical effects RCT (REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, ESCAPE, and MR CLEAN) of intravenous thrombolysis bridging intravascular mechanical thrombectomy and balloon dilatation within 6 hours after stroke, [40-44]) 5 excluded patients with blood pressure levels greater than 185/110mmHg. In another study (ESCAPE study) [25], there were no exclusion criteria for blood pressure level. The DAWN study also took > 180/100mmHg as one of its exclusion criteria [26].Although these RCTs do not clearly explain the reason for setting this blood pressure value, it is reasonable to recommend this value as a guideline at present according to their research results.

Recommendations

[1] Patients with elevated blood pressure and other aspects suitable for intravenous rt-PA therapy should be cautious in lowering blood pressure before thrombolysis. The recommended goal systolic blood pressure is <180 mm Hg and diastolic blood pressure is <105 mm Hg (Class I, Level of Evidence B).

[2] It is reasonable to maintain blood pressure (≤180/100 mm Hg) before intra-arterial therapy in patients who do not receive IV thrombolysis (Class II, Level of Evidence B).

[3] Within 24 hours after IV R t-PA thrombolysis, blood pressure should be <180/105 mm Hg (Class I, Level of Evidence B).

5. Blood glucose control

(1) Hyperglycaemia: About 40% of patients have hyperglycemia after stroke, which is unfavourable for prognosis. Insulin therapy should be given when blood glucose exceeds l0 mmol/l. Blood glucose monitoring should be strengthened, and the blood glucose level can be controlled at 7.7--10 mmol/L.

(2) Hypoglycaemia: When blood glucose is lower than 3.3mmol/L, 10%--20% glucose can be given orally or intravenously. The goal is to reach normal blood glucose levels.

(III) rt-PA administration dose and method

Rt-PA 0.9mg/kg (the maximum dose is 90mg) is injected intravenously, of which 10% is injected intravenously within the first 1min, and the rest 90% is dissolved in 100ml of normal saline for continuous intravenous drip of 1 hour. Patients should be closely monitored during medication and within 24 hours of medication (Supplemental Table 6).

(IV) Other recommendations

Age, baseline NIHSS, vascular recanalization and sICH are the main factors affecting prognosis. The observational meta-analysis showed that compared with patients aged < 80 years, AIS patients aged > 80 years have 50% less chance of obtaining a good prognosis. However, another meta-analysis on six RCTs showed that intravenous rt-PA thrombolysis was still beneficial compared with no thrombolysis in AIS patients aged > 80 years with the onset < 3h (*OR* = 1.4, 95% *CI:* 1.3--1.6, *n*=3439).

Advanced age and high stroke severity at baseline are important predictors of poor prognosis. However, according to IST-3 research and meta-analysis, the benefits of rt-PA intravenous thrombolysis for severe AIS at baseline have not decreased. In the analysis after the NINDS study, it was found that intravenous thrombolysis for mild stroke can still produce benefits when the onset is < 3 h [72-73]， and meanwhile, the risk of cerebral infarction haemorrhage conversion is low.

The EXCHANTED study did not prove that the low dose (0.6mg/kg) rt-PA and standard dose (0.9mg/kg) are equally effective (*OR*=1.09, 95% *CI:* 0.95--1.25), but

the risk of bleeding is reduced (*OR*=0.48, 95% *CI:* 0.27--0.86) [74].

The proportion of thrombocytopenia in the population is about 0.3%. The proportion of INR abnormality is about 0.4% in patients who have not taken warfarin and have no history of suspected coagulation mechanism abnormalities such as end-stage renal disease and tumour [75].The sample size of intravenous rt-PA thrombolysis study for patients with low molecular weight heparin was small, but the results showed that the sICH risk increases (*OR*=8.4, 95% *CI:* 2.2--32.2), death risk increases (*OR*=5.3, 95% *CI:* 1.8--15.5), and the proportion of good prognosis decreases by 68% [76].

The observational study shows that baseline MRI indicates microbleeds and increased sICH risk after intravenous rt-PA thrombolysis (*RR*=2.36, 95% *CI:* 1.21--4.61). When the number of microbleeds is > 10, the risk of sICH is significantly increased (*RR*=7.01, 95% *CI:* 3.20--15.38). Since the proportion of microbleeds > 10 is less than 1%, it is not recommended to perform conventional MRI before intravenous thrombolysis to exclude microbleeds [77]**.**

Evidence for the combined use of IIb/IIIa receptor antagonists such as abciximab and rt-PA intravenous thrombolysis is insufficient.[78]**.**The retrospective case-control study shows that early antithrombotic therapy within 24 hours after intravenous thrombolysis may be safe, and the risk of haemorrhage is not increased.

Recommendations

Recommendation	**Class of Recommendation**

	Level of Evidence
Within 3 hours of onset, rt-PA IV thrombolytic therapy is recommended for patients aged over 18 and who meet other criteria	**Class I, Level of Evidence A**
For patients who are suitable for IV thrombolysis within 3 hours of onset, rt-PA IV thrombolysis is recommended (drug dose 0.9 mg/kg, maximum dose 90 mg, continuous infusion within 60 minutes, of which 10% of the first dose is IV infusion within 1 minute)	**Class I, Level of Evidence A**
For AIS patients with severe symptoms within 3 hours of onset, rt-PA IV thrombolysis is recommended. Although the risk of bleeding events increases, it still benefits	**Class I, Level of Evidence A**
For patients with mild symptoms but with disabling stroke symptoms within 3 hours of onset, rt-PA IV thrombolytic therapy is recommended. Current studies have shown that rt-PA IV thrombolytic therapy is beneficial for these patients	**Class I, Level of Evidence B**
rt-PA IV thrombolysis is still recommended for patients suitable for IV thrombolysis within 3-4.5 hours of onset	**Class I, Level of Evidence B**
The benefit of rt-PA thrombolytic therapy for AIS patients aged over 80 years within 3-4.5 hours after onset is not clear	**Class IIb, Level of Evidence B**
Within 4.5 hours of AIS onset, low dose IV rt-PA can be given	**Class IIb, Level of Evidence B**

to patients with potential high risk of haemorrhagic events. Usage: rt-PA 0.6 mg/kg (maximum dose is 60 mg), of which 15% of the total amount was intravenously injected within the first 1 minute, and the remaining 85% was intravenously infused with infusion pump for 1 hour	
Considering the low incidence of platelet abnormalities and coagulation dysfunction in the general population, IV thrombolysis should not be delayed while waiting for the results of platelet counts when there is no reason to suspect that the results of the tests are abnormal	**Class IIa, Level of Evidence B**
The safety and efficacy of intravenous rt-PA therapy in AIS patients with potential bleeding risk or coagulation disorders have not been determined the safety and efficacy of IV rt-PA therapy in AIS patients with potential haemorrhagic risk or coagulation disorders have not been determined	**Class III, Level of Evidence C**
IV rt-PA is not suitable for patients who have used low molecular weight heparin within 24 hours, regardless prophylactic or therapeutic dose	**Class III, Level of Evidence B**
Pre-thrombolytic MRI examination showed that IV thrombolysis was reasonable in patients with a number of (1-10) cerebral microbleeds	**Class IIa, Level of Evidence B**

Pre-thrombolytic MRI examination showed that IV thrombolysis was associated with an increased risk of symptomatic intracerebral hemorrhage in patients with a number of (>10) cerebral microbleeds, and the clinical benefit is not clear. If there may be significant potential benefits, IV thrombolysis may be reasonable	**Class IIa, Level of Evidence B**
During IV thrombolysis, physicians should be fully prepared to respond to emergency adverse reactions, including hemorrhagic complications and vasogenic edema that may cause airway obstruction	**Class I, Level of Evidence B**
Abciximab cannot be used concurrently with IV rt-PA	**Class III, Level of Evidence B**
Whether or not the endovascular treatment is bridged, the risk of starting antiplatelet therapy within 24 h after IV thrombolysis remains unclear.	**Class IIb, Level of Evidence B**

In some specific cases, there is a lack of high-level evidence-based medical evidence such as RCT or cohort studies in terms of the benefits or risks of thrombolysis. However, there is consensus among most experts as follows for reference.

Recommendation

Recommendation	Class of Recommendation Level of Evidence
The time from onset to treatment has a major impact on prognosis, and rt-PA IV thrombolysis cannot be postponed to wait if symptoms are relieved	**Class IIa, Level of Evidence C**
For patients with mild non-disabling AIS, IV rt-PA therapy may be suitable within 3 hours of onset	**Class IIa, Level of Evidence C**
IV rt-PA may be beneficial for AIS patients who had a history of digestive tract or urinary bleeding	**Class IIa, Level of Evidence C**
AIS IV thrombolysis may be considered within 14 days after surgery, but should weigh the benefit of thrombolysis and the risk of hemorrhage of the surgical site	**Class IIb, Level of Evidence C**
AIS patients with recent major trauma history (within 14 days, without affecting the head), physician should carefully consider IV rt-PA treatment and should weigh the risk of the wound hemorrhage and the severity of stroke and subsequent disability	**Class IIb, Level of Evidence C**

The safety and efficacy of IV rt-PA therapy in patients with AIS who have a history of vascular perforation within 7 days are not known	**Class IIb, Level of Evidence C**
AIS patients with lumbar puncture within 7 days, the safety of IV rt-PA therapy is uncertain	**Class IIb, Level of Evidence C**
AIS patients with abnormal baseline glucose [< 50 mg/dl (2.78 mmol/L) or > 400 mg/dl (22.2 mmol/L)], followed by normalized blood glucose, the benefit of IV rt-PA is not determined	**Class IIb, Level of Evidence C**
AIS patients with convulsions may benefit from IV rt-PA therapy if there is evidence that limb dysfunction is due to stroke rather than paralysis after seizures	**Class IIa, Level of Evidence C**
AIS patients who have a known or suspected extracranial carotid artery dissection with an onset time <4.5 h, IV rt-PA therapy should be chosen carefully	**Class IIa, Level of Evidence C**
AIS patients who have a known or suspected intracranial carotid artery dissection, the efficacy and safety of IV rt-PA therapy has not been established	**Class IIb, Level of Evidence C**
AIS patients with a small or moderate (<10 mm) unruptured intracranial aneurysm, IV rt-PA therapy may be	**Class IIa, Level of Evidence C**

considered may be considered	
AIS patients with large unruptured or unstable intracranial aneurysms, the risk and effectiveness of IV rt-PA thrombolysis is uncertain	**Class IIb, Level of Evidence C**
AIS patients with unruptured or untreated intracranial vascular malformations, the safety and risk of IV rt-PA therapy is not known	**Class IIb, Level of Evidence C**
AIS patients with neuroectodermal tumours may benefit from IV rt-PA thrombolysis	**Class IIa, Level of Evidence C**
AIS with acute myocardial infarction may be considered for intravenous thrombolysis according to the appropriate rt-PA dose of AIS, followed by PCI or stent for acute coronary syndrome AIS patients with acute myocardial infarction may be considered for IV thrombolysis with the appropriate rt-PA dose of AIS, followed by PCI or stent for acute coronary syndrome	**Class IIa, Level of Evidence C**
AIS patients with recent myocardial infarction (>3 months), rt-PA thrombolysis may be beneficial if there is also a non-ST elevation myocardial infarction, or ST elevation myocardial infarction involving the right ventricle/inferior wall	**Class IIa, Level of Evidence C**

AIS combined with recent myocardial infarction (>3 months), if ST elevated, and involving the left ventricle/anterior wall, the safety and risk of IV rt-PA thrombolysis is uncertain	**Class IIb, Level of Evidence C**
Severe AIS with acute pericarditis which may lead to severe disability (mRS score 3 to 5 points), the benefit of IV rt-PA thrombolysis is not clear. An urgent cardiologist consultation is required	**Class IIb, Level of Evidence C**
Mild or moderate AIS with acute pericarditis or left atrial/ventricular thrombus, the risk and benefit of IV rt-PA thrombolysis is unknown	**Class III, Level of Evidence C**
Severe AIS with left atrial/ventricular thrombus, or atrial myxoma, or papillary fibroids, may have severe disability (mRS score 3 to 5 points). The safety and efficacy of IV rt-PA are unknown	**Class IIb, Level of Evidence C**
AIS with cardiovascular or cerebrovascular DSA, IV rt-PA thrombolysis may be benefit. Patients should be carefully assessed for indications, contraindications, and relative contraindications	**Class IIa, Level of Evidence A**
The efficacy and safety of IV rt-PA thrombolysis in AIS patients with malignancy is unknown. If the expected survival period is >6 months, no other contraindications, no coagulation abnormalities or bleeding, careful consideration of IV	**Class IIb, Level of Evidence C**

rt-PA thrombolysis is suitable	
Pregnant women with moderate or severe stroke may benefit from intravenous rt-PA thrombolysis if the benefits of intravenous thrombolysis outweigh the risk of uterine bleeding.	**Class IIa, Level of Evidence C**
The evidence of benefit and risk of IV rt-PA thrombolysis for AIS patients within 14 days postpartum is insufficient	**Class IIb, Level of Evidence C**

(V) Other thrombolytic drugs

In addition to rt-PA, different studies have evaluated the efficacy and safety of intravenous thrombolysis with urokinase (UK), desmoteplase, TNK-tPA and ultrasound-assisted intravenous thrombolysis respectively [81]. A study shows that thrombolysis with urokinase is relatively safe and effective in AIS within 6 hours of onset [32]. In the desmoteplase study (DIAS-3), after the AIS patients with severe stenosis or macrovascular occlusion 3--9 hours after onset were given desmoteplase (90 μg/kg) or placebo, there was no statistical difference in efficacy and safety between them. Desmoteplase did not improve the efficacy or increase the proportion of bleeding [98]. In the ultrasound-assisted intravenous thrombolysis study (NOR-SASS), the AIS patients within 4.5h hours of onset were given TNK-tPA or rt-PA intravenous thrombolysis, and then randomly divided into the treatment group or placebo group. There was no statistical difference in the efficacy endpoint (24h NIHSS improvement rate and 90d neurological function outcome) or safety endpoint (sICH) between the two groups [79].

Recommendations

[1] Urokinase is safe for those who are not suitable for rt-PA treatment within 6 hours of onset. However, the validity needs further confirmation by high quality large sample size RCT (Class IIb, Level of Evidence B).

[2] It has not been confirmed that IV injection of tenecteplase thrombolysis (single dose of 0.4 mg/kg) is superior or inferior to rt-PA. However, for patients with mild neurological dysfunction without occlusion of the intracranial artery, tenecteplase can be considered instead of rt-PA (Class IIb, Level of Evidence B).

[3] In addition to clinical trials, ultrasound thrombolysis is not recommended as an adjunct therapy to IV thrombolysis. Desmoplatinolytic thrombolysis is not recommended under imaging guidance (Class III, Level of Evidence B).

II. Patients within 6 hours of onset-bridging/intravascular treatment

In the PROACT-II study, the patients with middle cerebral artery (M_1 or M_2) occlusion within 6 hours of onset were given recombinant prourokinase combined with heparin arterial thrombolysis (experimental group) or heparin-only arterial thrombolysis (control group) respectively. The proportion of 3-month good neurological function prognosis (mRS score 0--2) in the primary endpoint of the experimental group was higher than that in the control group (40% vs. 25%, P = 0.04). The recanalization rate of middle cerebral artery (MCA) in the experimental group was higher than that in the control group (66% vs. 18%, P< 0.001). However, the incidence rate of symptomatic cerebral haemorrhage in the experimental group was higher than that in the control group (10% vs. 2%, P=0.06), and the mortality rate of the two groups was similar.

The MELT trial compared the effect of drug therapy (treatment group) and urokinase

therapy for artery within 6 hours. The incidence rate of good neurological prognosis (mRS score 0--2) in 3 months in the treatment group was higher than that in the control group (49.1% vs. 36.8%, *P*=0.35). The overall treatment effect and the incidence rate of symptomatic cerebral haemorrhage were consistent with PROACT-II trial [80,81].

The early exploratory experiment used a small sample study to evaluate the efficacy of intravenous low-dose rt-PA combined with arterial thrombolysis. According to the research results of Emergency Management of Stroke (EMS), Interventional Management Study I (IMS I) and Interventional Management Study II (IMS II), the neurological function prognosis of the combined treatment group was significantly better than that of the control group [82-84].The Basilar Artery International Cooperation Study (BASICS) reviewed and analysed the clinical effects of antithrombotic therapy, intravenous thrombolytic therapy or arterial thrombolytic therapy for patients with acute onset of basilar artery occlusion, and did not show significant differences among various therapeutic schemes [85].

The recent intravascular trial suggested that arterial thrombolysis has limited effect, but it can also be used as salvage therapy instead of main therapy. Among 141 patients in the THRACE trial intervention group, 15 patients (11%) used alteplase in artery after mechanical thrombectomy, with an average dosage of 8.8mg. Compared with mechanical thrombectomy alone, it had no effect on clinical prognosis [44].

Bridging therapy refers to intra-arterial interventional reperfusion therapy based on

intravenous thrombolysis, which is divided into direct bridging therapy and salvage bridging therapy. Direct bridging refers to direct thrombectomy without observing and waiting for thrombolytic effect after intravenous thrombolysis. Salvage bridging refers to observing changes in neurological function of patients after intravenous thrombolysis, and further considering thrombectomy after failure of intravenous thrombolysis.

At present, intravenous thrombolysis is the first choice for patients within the intravenous thrombolysis time window. In five randomized controlled studies of early thrombectomy, more than 90% of patients were treated with mechanical thrombectomy bridging therapy based on intravenous thrombolysis. For the clinical effects of bridging therapy and direct thrombectomy, randomized controlled trials are underway. The subgroup analysis of the HERMES study shows that there is no difference in prognosis between patients treated with bridging therapy (n=1090) and patients treated with direct thrombectomy (n=188) (P=0.43), but most patients treated with direct thrombectomy are due to contraindications for intravenous thrombolysis [86]. SWIFT, STAR and other non-randomized controlled trials also suggest that direct thrombectomy and bridging therapy have similar results. Intravenous thrombolysis before mechanical thrombectomy does not improve clinical benefits compared with mechanical thrombectomy alone [87-89]. However, some studies suggest that bridging therapy has good prognosis, low mortality rate, high recanalization rate, less times of thrombectomy, shorter thrombectomy time and no increase in sICH risk [90-93].

In the recently published EXTEND-IA TNK study, after intravenous thrombolysis with TNK-tP before bridging therapy, the good reperfusion rate before thrombectomy can reach 22% for AIS patients with macrovascular occlusion within 4.5h hours of onset, which is significantly higher than the 10% reperfusion rate of alteplase (difference 12%, 95% *CI:* 2--21; incidence ratio: 2.2, 95% *CI:* 1.1--4.4; Non-inferiority $P = 0.002$; optimal efficiency $P=0.03$). There is no difference in sICH between the two groups, and the good prognosis of the TNK-tPA group is better after 90 days. The study suggests that the new intravenous thrombolytic drugs can increase the recanalization ratio of macrovascular occlusion before thrombectomy, thus achieve early recovery of perfusion and improvement of prognosis [94].

Mechanical thrombectomy device has received extensive attention because of its many theoretical advantages: rapid recanalization, lower haemorrhage conversion rate and prolonged stroke intervention time window [95]. The Food and Drug Administration (FDA) approved MERCI Retrieval™ (2004) and Penumbra Stroke Systems™ (2008) as the first generation of mechanical thrombectomy devices. In 2013, three trials were conducted to evaluate the treatment of AIS with intravascular mechanical thrombectomy- Interventional Management Study III (IMS III), Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) and A Randomized Controlled Trial on Intra-arterial and Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS EXPANSION), all of which reported negative results [96-98], and failed to manifest the advantages of intravascular

treatment. This may be due to the following reasons: there was a long delay between the occurrence of symptoms and treatment, the adopted imaging method failed to screen out the potential benefited population, the recanalization rate was lower than expected, and the older generation of thrombectomy equipment was applied.

The US FDA approved the Solitaire™ and Trevo™ stent thrombectomy devices in 2012. After confirming the efficacy and safety of the new-generation stent thrombectomy device, a number of randomized controlled trials with the new-generation stent thrombectomy device as the main equipment have confirmed the advantages of thrombectomy therapy compared with intravenous thrombolysis or drug therapy alone in patients with macrovascular occlusion. Since the end of 2014, a series of related studies have successively released relatively consistent research results: among the screened patients with anterior circulation macrovascular AIS, intravascular treatment centering on mechanical thrombectomy can bring definite benefits.

According to the results of 6 randomized controlled trials (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE) of mechanical thrombectomy centring on recyclable stents, the 2015 guidelines give the highest-level recommendations for thrombectomy to specific populations [44].

Recommendations

[1] Mechanical thrombectomy is strongly recommended for patients within 6h

after AIS if they meet all the following criteria: (1) pre-stroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; and (5) ASPECTS of ≥6. (Class I, Level of Evidence A)

[2] It is reasonable to initial treatment with intra-arterial thrombolysis within 6h after AIS caused by occlusions of the MCA for carefully selected patients who have contraindications or no clinical response to the use of IV rt-PA and couldn't perform mechanical thrombectomy (Class IIa, Level of Evidence B).

[3] Endovascular treatment should be performed as soon as possible after its indication. Patients eligible for IV rt-PA should receive IV rt-PA and direct perform bridging treatment for mechanical thrombectomy (Class I, Level of Evidence A).

[4] Mechanical thrombectomy should performed as the first line treatment for patients who have contraindications to the use of IV rt-PA (Class IIa, Level of Evidence A).

[5] Stent retrievers is indicated for mechanical thrombectomy as first choice (Class I, Level A). Other thrombectomy or aspiration devices approved by local health authorities may be used at the operators' discretion (Class IIa, Level of Evidence B).

[6] Mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin

puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs (Class IIb, Level of Evidence B).

[7] Mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (Class IIb, Level of Evidence C).

[8] Mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have pre-stroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Additional randomized trial data are needed (Class IIb, Level of Evidence B).

III. Patients within 6--24 hours of onset-intravascular treatment

Progress has been made in the research on mechanical thrombectomy since 2015. The publication of DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) has extended the time window for mechanical thrombectomy from

6 hours to 24 hours. The results of these two randomized controlled trials suggest that intravascular treatment with stent thrombectomy is still very effective for patients with acute stroke over 6 hours of onset after screening suitable patients through preoperative evaluation. To sum up, there is clear evidence to support the use of AIS intravascular therapy. The success rate and recanalization rate of different mechanical thrombectomy devices are high in randomized controlled trials using a new generation of thrombectomy devices. Accurate patient selection schemes and efficient reperfusion therapy technology are the keys for patients with acute macrovascular occlusion to benefit from intravascular therapy.

Recommendations

[1] In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended (Class I, Level of Evidence A).

[2] In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable (Class IIa, Level of Evidence B).

[3] Patients with acute basilar artery occlusion within 6 to 24 hours should be evaluated in centers with multimodal imaging and treated with mechanical thrombectomy or they may be treated within a randomized controlled trial for

thrombectomy approved by the local ethical committee (Class IIb, Level of Evidence B).

[4] The benefits of mechanical thrombectomy are uncertain for patients with acute large vascular occlusion for more than 24 hours (Class IIb, Level of Evidence C)

See Supplemental Table 7 for a summary of imaging screening criteria beyond time windows in different studies.

Section 4 Anti-platelet aggregation therapy for acute ischemic cerebrovascular disease

I. Monotherapy against platelet aggregation

(I) Aspirin

Two large-scale clinical trials have confirmed that aspirin can significantly reduce the mortality or disability rate at the end of follow-up, reduce recurrence, and only slightly increase the risk of symptomatic intracranial haemorrhage [99, 100]. A meta-analysis of 41283 ischemic stroke patients from 8 clinical studies shows that 160-300 mg aspirin within 48 hours of stroke onset can significantly reduce the risk of early stroke recurrence and achieve better long-term prognosis, and is not the main risk factor for early haemorrhage complications [101]. Another meta-analysis comparing aspirin with placebo shows that aspirin for long-term secondary prevention and treatment can significantly reduce the risk of stroke (haemorrhagic or ischemic stroke) by 15% [102].

There is still controversy about the ideal therapeutic dose of aspirin. A study from Canada believes that the dose of aspirin should be 130 mg/d [103]. In the UK-TIA trial in the UK, 300mg/d aspirin is as effective as higher doses [104]. In a low-dose aspirin study in Sweden, 75mg/d aspirin can reduce the incidence of stroke and mortality by 18%, with statistical significance [105]. At present, most neurologists recommend a dose of 50-325 mg/d.

The subgroup analysis of the NINDS study shows that thrombolysis effect is better

and incidence of adverse prognosis is lower for patients taking aspirin in the early phase, but the incidence of sICH is not statistically significant compared with that of patients not taking aspirin in the early phase [106]. Amaro et al reviewed 172 patients in the acute phase of ischemic stroke who received thrombolysis. Specifically, 139 of them received antiplatelet aggregation therapy within 24 hours, 33 received corresponding therapy after 24 hours as usual. The results showed that the vascular recanalization rate of the early antiplatelet aggregation treatment group was higher at 3 days, the neurological function of the patients in the early antiplatelet aggregation treatment group was significantly better than that of the conventional treatment group at 90 days, and there was no significant difference in sICH ratio between the two groups [107]. In another multicentre retrospective study in Europe, 3,782 (31.9%) of the 11,865 stroke patients who received intravenous thrombolysis were routinely treated with antiplatelet drugs, mostly aspirin (3,016 patients, accounting for 25.4%), The results showed that the incidence of sICH and short-term mortality in patients receiving antiplatelet aggregation therapy during thrombolysis were not significantly different from those who did not receive antiplatelet aggregation therapy during thrombolysis [108]. Therefore, for thrombolytic patients, early use of aspirin may improve the prognosis without increasing the probability of sICH.

A multi-centre, randomized, open study from Germany started intravenous aspirin therapy early 90min after intravenous thrombolysis compared with intravenous rt-PA alone. All stroke patients in the experimental group were treated with oral aspirin 24 h

after intravenous rt-PA. It was planned to include 800 patients. After 642 patients were studied, the trial was finished ahead of schedule because the incidence of symptomatic intracranial haemorrhage in the aspirin treatment group was extremely high. The result analysis showed that the possibility of symptomatic intracranial haemorrhage in the intravenous aspirin combined with rt-PA group was twice as high as that in the intravenous rt-PA group alone, and there was no significant difference in the 90-day outcome between the two groups (mRS score 0-2 points).

(II) Clopidogrel

Clopidogrel is a prodrug. Active metabolites of clopidogrel irreversibly bind to ADP receptors on the surface of platelets, thus inhibiting platelet aggregation. A randomized controlled trial (CAPRIE) has confirmed that the incidence of vascular events (ischemic stroke, myocardial infarction or vascular death) after clopidogrel 75mg/d treatment was significantly lower than aspirin 75mg/d treatment [109]. Compared with aspirin, clopidogrel has obvious advantages in symptomatic atherosclerotic patients with a higher risk of recurrence of cardiovascular and cerebrovascular diseases within 3 years of follow-up [110]. A meta-analysis shows that clopidogrel reduces the risk of stroke recurrence by 32% compared with placebo, but the recurrence rate still reaches 8.5% [111], The reason may be related to clopidogrel resistance, and its incidence rate is as high as 31% [112]. The carrying rate of *CYP2C19* intermediate metabolism and slow metabolism in Asian population is much higher than that in European and American population.

A single oral dose of 300-600 mg clopidogrel can rapidly inhibit platelet aggregation. A preliminary prospective study included 20 patients with an average onset time of 25h after stroke, who were given clopidogrel 600mg orally. No deterioration of neurological function or intracranial haemorrhage was reported [113].

(III) Ticagrelor

Ticagrelor is an antiplatelet drug, whose mechanism of action is reversible binding with P2Y12 receptor on the surface of platelet membrane, inhibiting ADP-mediated platelet aggregation, and is not affected by *CYP2C19* genotype. In the ONSET/OFFSET study that compared the antiplatelet effect of clopidogrel, ticagrelor took effect faster and had stronger effect, and platelet function recovered faster after withdrawal of the drug [114]. In the RCT named PLATO, the analysis results of the stroke /TIA subgroup (n=1152) showed that ticagrelor had a tendency to reduce the primary outcome events and mortality compared with clopidogrel [115].The 2016 SOCRATES study showed that there was no significant difference in the incidence of major endpoint events (including haemorrhagic stroke or ischemic stroke, myocardial infarction and death) between ticagrelor and aspirin for AIS or TIA patients (P=0.07). However, in the secondary endpoint analysis, ticagrelor can significantly reduce the recurrence of ischemic stroke by 13%(P=0.046) [116]. The subgroup analysis results of the SOCRATES study shows that among Asian patients with TIA and minor stroke, the risk of stroke recurrence, myocardial infarction or death is lower in the ticagrelor group (10.6% vs. 5.7%, P< 0.01), and there is no difference in major bleeding risk

between the two groups (0.6% vs. 0.8%, HR=0.76, 95% *CI:* 0.36-1.61). The subgroup analysis results of another SOCRATES study show that patients with AIS or TIA accompanied by ipsilateral intracranial artery stenosis are at a lower risk of stroke recurrence, myocardial infarction or death than the aspirin group (HR=0.68, 95% *CI:* 0.53-0.88, *P*=0.003) [117].

(IV) Cilostazol

Cilostazol can reversibly inhibit platelet aggregation and antithrombotic formation, inhibit vascular smooth muscle cell proliferation and protect vascular endothelial cells by inhibiting the activity of cyclic nucleotide phosphodiesterase-3 (PDE-3) and inhibiting the degradation of cyclic adenosine monophosphate (cAMP).

Huang Yining et al [118] conducted a randomized, double-blind prospective study (CASISP), where 720 patients were randomly divided into two groups, treated with aspirin and cilostazol respectively. The results show that both drugs can reduce the recurrence rate of stroke without obvious difference, but the incidence rate of haemorrhagic complications in the cilostazol group is significantly lower, suggesting cilostazol is more suitable for cerebral infarction patients with higher risk of haemorrhage. In the CSCP Phase-II study, 2,672 patients were enrolled in 278 hospitals in Japan, including 1337 patients in the cilostazol group and 1335 patients in the aspirin group. The number of patients requiring hospitalization due to various stroke events in the cilostazol group was significantly lower than that in the aspirin group. The study believes that cilostazol is no worse than aspirin in secondary

prevention of ischemic stroke, and has fewer bleeding events, and can be taken on a long-term basis [119].

(V) Indobufen

Indobufen exerts antiplatelet effect by reversibly inhibiting COX-1 and inhibiting platelet aggregation induced by ADP, epinephrine, collagen and arachidonic acid [120]. In addition, it can also reduce platelet factor 3 and platelet factor 4, significantly inhibit coagulation factor II and coagulation factor X, and has anticoagulant effect [121].

A study conducted a one-year follow-up of 270 patients with TIA who took indobufen (100mg/ time, bid), and the results showed that the incidence of TIA was significantly reduced after one-month treatment ($P< 0.001$) [122]. In addition, a domestic study randomly divided 170 patients with acute cerebral infarction into the indobufen group and aspirin group to compare clinical effects. The results showed that the neurological impairment scores of the two groups were significantly improved, and there was no statistical difference. The incidence of adverse reactions possibly related to taking of indobufen and aspirin were 2.4% and 5.7% respectively, and indobufen was relatively safe to use during acute cerebral infarction [123].

The post-marketing monitoring study of indobufen included 5,642 patients with atherosclerotic ischemic vascular disease, 40% of whom took 200mg of indobufen daily, 60% of whom took 400mg of indobufen daily, 76% of whom took continuous treatment for at least 3 months. During the study, 220 patients (3.9%) had adverse

reactions. Specifically, the incidence of gastrointestinal adverse reactions was 3.8%, and the incidence of haemorrhage-related events was only 0.38% [124].

A meta-analysis involving 19 RCTs with a total of 5,304 patients found that 7 RCTs reported the incidence of stroke. The analysis results showed that indobufen was not statistically significant from aspirin and warfarin in the incidence of stroke. Compared with aspirin, indobufen has a lower incidence than the aspirin group in terms of haemorrhage, gastrointestinal reaction and total adverse drug events [125].

(VI) Abciximab

In 2000, neurological researchers at the University of Iowa conducted a prospective, multi-center, double-blind, placebo-controlled study on the safety (24-hour symptomatic/asymptomatic cerebral haemorrhage) and efficacy (3-month mRS score, Barthel index) of abciximab [126]. The study found that the safety of abciximab was similar to placebo and did not significantly improve the 3-month functional prognosis. The ABeSTT trial was a global, double-blind, placebo-controlled RCT. After 808 AIS patients were enrolled, it was terminated earlier due to the unsatisfactory benefit-risk ratio of abciximab. Intravenous administration of abciximab did not improve the functional prognosis of patients, and increased the risk of intracranial haemorrhage [127].

There was a trial in 2002 and 2010 respectively that evaluated the safety and efficacy of intravenous thrombolysis combined with abciximab for AIS patients. Lee et al[128] found in a small sample pre-study in 2002 that intravenous thrombolysis combined

with abciximab can significantly improve the functional prognosis of patients without increasing the risk of bleeding. This conclusion needs further confirmation in large-scale prospective studies. In 2010, Gahn et al [78] conducted a trial of reduced thrombolysis combined with abciximab in the treatment of AIS and reached a similar conclusion. The sample size of the above two studies was less than 30 patients, resulting in low referability. There is no prospective, multicenter RCT on the secondary prevention and treatment effect of abciximab on cerebral infarction in China.

(VII) Tirofiban

Tirofiban is a platelet surface glycoprotein IIb/III receptor antagonist. Kellert et al[129]found that the risk of adverse prognosis and bleeding of bridging tirofiban was increased compared with thrombectomy alone in a prospective cohort study released in 2013 on bridging tirofiban for antithrombotic treatment after mechanical thrombectomy.

Lin et al [130] In the antithrombotic study on AIS patients beyond thrombolytic time window released in 2017, tirofiban was found to improve functional prognosis without increasing bleeding risk compared with aspirin or clopidogrel. The results of the 25-sample study need to be further verified in large-sample prospective trials. The SaTIS trial was a prospective, multicenter, placebo-controlled, open-label RCT with a total of 260 samples. The study found that tirofiban did not significantly improve the functional prognosis compared with placebo, but did not increase the risk of bleeding

and could reduce mortality [131].

In recent years, the research on tirofiban bridging thrombectomy/thrombolysis, combined with anticoagulant drugs/other antithrombotic drugs has a significant growth trend in China. In 2017, two retrospective cohort studies in China found that small-dose intravenous tirofiban did not increase the risk of haemorrhage after mechanical thrombectomy [132]. One of the trials proved that this treatment method can improve the prognosis of patients [133]. In 2017, Liu Zhiqiang et al [134]carried out a comparative evaluation trial on the safety and efficacy of antithrombotic therapy for recurrent TIA. The trial found that tirofiban bridging clopidogrel+aspirin dual antibody can obtain better curative effect and reduce adverse reactions compared with clopidogrel+aspirin dual antibody alone, which is more worthy of promotion. In 2017, Wang Sheng et al [135]carried out a trial on antithrombotic therapy for progressive stroke (tirofiban bridging clopidogrel+aspirin dual antibody, compared with clopidogrel+aspirin dual antibody alone), and the researchers also reached similar conclusions.

(VIII) Eptifibatide

Eptifibatide selectively blocks the binding of adhesion protein to glycoprotein IIb/IIIa. The CLEAR study is a prospective, multi-center, double-blind RCT. The study found that there is no significant difference in safety and efficacy between low-dose intravenous thrombolytic bridging eptifibatide and standard thrombolytic therapy, and the standard-dose thrombolytic therapy shows a trend of better efficacy.

The CLEAR researchers conducted a post hoc analysis and propensity matched analysis on a series of studies conducted in 2008, 2013 and 2014 [136]. It found that low-dose intravenous thrombolysis bridging eptifibatide is not superior to standard thrombolysis in improving the 90d mRS score, and further confirmation by prospective RCT is needed. In 2015, the CLEAR researchers conducted a single cohort, open-label multi-center trial [137]. The trial found that the safety of standard-dose thrombolytic bridging eptifibatide seems to need further confirmation by prospective RCT. There is still a lack of prospective, multicenter RCT of eptifibatide for secondary prevention of cerebral infarction in China.

Recommendations

[1] Aspirin is recommended for patients with AIS within 24 to 48 hours after onset. For patients treated with IV rt-PA, aspirin is usually delayed until 24 hours later (Class I, Level of Evidence A).

[2] Aspirin (50-325 mg/d) or clopidogrel (75 mg/d) alone can be used as primary antiplatelet drug therapy (Class I, Level of Evidence A).

[3] Aspirin therapy is not recommended as an alternative therapy for AIS patients who are suitable for rt-PA IV thrombolysis or mechanical thrombectomy (Class III, Level of Evidence B).

[4] Ticagrelor (instead of aspirin) is not recommended for acute mild stroke (Class III, Level of Evidence B).

[5] Cilostazol can be used in AIS patients as an alternative to aspirin if aspirin or clopidogrel is not available (Class IIa, Level of Evidence A).

[6] For high risk of ischemic stroke patients with aspirin intolerance (gastrointestinal adverse reactions or allergies, etc.), indobufen (100 mg per time, twice a day) is feasible (Class IIb, Level of Evidence B).

[7] Abciximab is not recommended for AIS (Class III, Level of Evidence B).

[8] Tirofiban is safe in the perioperative period for bridging therapy or endovascular therapy. The recommended dose is 0.1-0.2 ug/(kg•min) and continuous infusion should be limited in 24 hours (Class IIa, Level of Evidence B).

[9] The efficacy of tirofiban and eptifibatide has not been fully determined, and further studies are needed to confirm (Class IIb, Level of Evidence B).

II. Dual antiplatelet therapy

(I) Clopidogrel combined with aspirin

The study of Fast Assessment of Stroke and TIA to Prevent Early Recurrence (FASTER) randomly grouped the TIA or mild ischemic stroke patients within 24 hours of onset, and gave aspirin combined with clopidogrel dual antiplatelet therapy and aspirin monotherapy to them to observe and compare the 90d clinical prognosis of the patients. The results showed that the 90-day stroke risk of patients receiving combined therapy was 7.1%, compared with 10.8% in the monotherapy group. Early

dual antiplatelet therapy reduced the absolute risk of stroke recurrence and did not increase the risk of intracranial haemorrhage. The trial was stopped because the case collection was too slow and no definite conclusion could be reached [138]. The study of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) The study showed that in patients with recent ischemic stroke or high-risk TIA, after a follow-up of 3.5 years, it was found that the primary outcome events (including ischemic stroke, myocardial infarction, vascular death and readmission due to acute ischemic events) of aspirin combined with clopidogrel treatment group had no significant difference from the clopidogrel monotherapy group (P=0.224), but increased the risk of massive haemorrhage and fatal haemorrhage [139]. In the secondary prevention (SPS3) study of AIS subcortical minor stroke, there was no significant difference in the recurrence rate of ischemic stroke disability or fatal stroke between the clopidogrel combined with aspirin (325mg/d) group and aspirin monotherapy group, but the haemorrhage and death risks of the combined therapy group were significantly increased [140]. Dual antiplatelet therapy was not recommended in the global guidelines before 2011 for patients with ischemic stroke. The release of the 2013 study of Clopidogrel and Aspirin versus Aspirin Alone for the Treatment of High—risk Patients with Acute Non-disabling Cerebrovascular Event (CHANCE) has changed this status.

The CHANCE study included 5170 patients with acute mild ischemic stroke or TIA with high recurrence risk, and compared the efficacy and safety of clopidogrel

combined with aspirin dual antiplatelet therapy and aspirin monotherapy. The patients in the trial group were treated with clopidogrel for 3 months (the loading dose on the first day was 300mg, then 75mg/d) and aspirin (75mg/d) was used 21 days before the combination, while the patients in the control group were treated with aspirin (75mg/d) alone. The results showed that compared with aspirin alone, the dual antiplatelet therapy group reduced the relative risk of 90 days stroke by 32%, reduced the absolute risk by 3.5%, and did not increase the haemorrhage risk. The CHANCE study confirmed that compared with aspirin monotherapy, clopidogrel combined with aspirin can significantly reduce the 90-day stroke recurrence risk without increasing the incidence of moderate and severe haemorrhage in high-risk patients with acute non-disabling cerebrovascular events [141]. Meta-analysis data show that short-term aspirin combined with clopidogrel is more effective than monotherapy and does not increase the risk of haemorrhage [142]. Two randomized controlled trials published in 2014 and 2015 both confirmed that aspirin combined with clopidogrel antiplatelet in early AIS was superior to aspirin alone in reducing the deterioration and recurrence of the nervous system in the early phase [143]. The POINT study published in May 2018 showed that compared with aspirin alone, clopidogrel combined with aspirin dual antiplatelet therapy can reduce the risk of severe ischemic events in patients with mild ischemic stroke or high-risk TIA [162]. The results of the CHANCE study have been confirmed in European and American population. All the above studies have confirmed that aspirin combined with clopidogrel in the early phase is superior to

aspirin alone in reducing the recurrence of stroke and improving the prognosis of neurological function.

(II) Dipyridamole combined with aspirin

In 1999, Millan-Guerrero et al [145]found that comparing dipyridamole intravenously given to AIS patients 24 hours after onset with oral aspirin, aspirin was more advantageous in improving functional prognosis. Haungsaithong et al[146] in a small-sample RCT, it was found that aspirin combined with dipyridamole antiplatelet therapy had no advantage in AIS treatment compared with aspirin, clopidogrel and cilostazol antithrombotic monotherapy. In contrast, clopidogrel could significantly improve the NIHSS score of stroke patients in the 4th week after onset.

In 2005 and 2010, Chairangsarit and Dengler et al compared the therapeutic effects of aspirin combined with dipyridamole dual antithrombotic therapy and aspirin respectively. Chairangsarit[147] in a pre-test with a sample size of 38, it was found that aspirin combined with dipyridamole in 48 hours after onset could significantly improve neurological impairment symptoms 6 months after onset of the disease than aspirin antithrombotic therapy, but there was no significant difference in reducing recurrence rate between the two. Dengler et al[148] in a prospective, multi-center and large-sample study, found that after aspirin and dipyridamole were given to AIS or TIA patients within 24 hours of onset, there was no significant difference in improvement of 90d mRS score, vascular events, etc. compared with aspirin monoclonal antibody first given for 7 days and then changed to dual antithrombotic

therapy. In the subgroup analysis of the PRoFESS research published in 2010, Bath et al [149] found that aspirin combined with sustained-release dipyridamole had similar effects in improving functional prognosis, recurrence rate and mortality rate, and had no statistical difference in safety compared with clopidogrel.

There is still a lack of prospective, multicenter RCTs of dipyridamole for secondary prevention of cerebral infarction in China. Liang Tao et al [150] found that aspirin combined with dipyridamole was more effective and safe in preventing cerebral infarction than aspirin alone in a case-control trial with a sample size of 178 in 2010.

Recommendations

[1] For patients with mild stroke and high-risk TIA who did not receive IV thrombolysis, dual antiplatelet therapy [aspirin 100 mg/d, clopidogrel 75 mg/d (first day load dose 300 mg)] was initiated within 24 hours of onset and lasted for 21 days, then clopidogrel 75 mg/d which could significantly reduce stroke recurrence for 90 days (Class I, Level of Evidence A).

[2] The efficacy of dipyridamole alone or dipyridamole combined with aspirin of preventing the recurrence of ischemic stroke still needs RCTs to confirm (Class IIb, Level of Evidence B).

III. Triple antiplatelet therapy

The TARDIS study released in 2017 compared the effects of triple antibody (aspirin,

clopidogrel and dipyridamole) and monoclonal antibody (clopidogrel) or double antibody (aspirin combined with dipyridamole) treatment on the recurrence rate and severity of stroke and TIA within 90 days. Specifically, the treatment time of triple antibody was 30 days, and the antiplatelet treatment schemes of the two groups were the same after 30 days. The subjects of the study were acute non-cardiogenic ischemic stroke and TIA patients over 50 years old, who were randomly assigned to the experimental group and control group. The median time of randomization was 29.3h. The study plannned to include 4,100 patients and was stopped after 3,096 patients were included. The reason was that although there was no statistical difference in the recurrence rate and severity within 90 days (95%*CI:* 0.67-1.20, *P*=0.47) between the triple treatment group and the single or dual treatment group, the incidence rate of bleeding complications in the triple treatment group was 20%, and the incidence rate of bleeding complications in the monoclonal antibody/double antibody therapy group was 9%, with statistical difference (*P*< 0.001, 95%*CI:* 1.25-3.96) [151, 152]. Considering that 11% of the patients in the TARDIS trial had a NIHSS score of > 6, and 10% of the patients had received thrombolytic therapy before randomization, which may affect the results. In addition, in the TARDIS subgroup analysis, patients with mild stroke had higher benefits (*P*=0.09). Whether limiting the inclusion criteria to minor stroke and giving triple antibody therapy is more meaningful than monoclonal antibody/double antibody therapy still need further trials and discussions. The randomization time of 70% patients in the TARDIS trial was 24-48h after onset.

Further attention should be paid to whether the delay in starting the triple antibody time window will affect the randomization time, and to the subgroup analysis within 24h after onset and 24h after onset. In addition, the CHANCE, SOCRATES and TIAregistry.org suggest that most patients relapse within 8-10 days after onset. The TARDIS study limits the duration of triple antibody to 30 days to be too long, and adjusts it to 8-10 days to reduce the incidence of bleeding complications. Further clinical research is needed.

Recommendations

Triple antiplatelet aggregation therapy (aspirin, clopidogrel and dipyridamole) are not recommended for the treatment of acute non-cardiogenic stroke and TIA (Class III, Level of Evidence B).

See Supplemental Table 8 for a summary of commonly used antiplatelet drugs for acute ischemic stroke.

Please refer to Figure 4 for details of the anti-platelet aggregation treatment process for patients with acute ischemic stroke.

Section 5 Other treatment in acute phase

I. Neurovascular protection

Several studies have shown that butylphthalide could improve collateral circulation and rescue the penumbra [153-155]. The results of multi-centre randomized controlled trials showed that butylphthalide was safe and effective in the treatment of acute cerebral infarction, and could improve neurological impairment and daily living ability. A meta-analysis involving 21 trials (2123 patients) has also confirmed that butylphthalide could effectively improve neurological impairment in AIS patients with few or no serious adverse reactions [156].

In a multicentre, randomized, double-blind, placebo-controlled trial that evaluated intravenous use of human urinary kallidinogenase (Urinary Kallidinogenase) in patients with acute cerebral infarction, the human urinary kallidinogenase treatment group showed greater improvements in functional outcomes and was safer than the placebo group [157].

Vinpocetine can selectively expand cerebral vessels by inhibiting phosphodiesterase type I enzyme, reduce cerebral vascular resistance, increase cerebral blood flow perfusion in focal areas, increase consumption and utilization of glucose and oxygen in brain tissues without affecting systemic circulation (blood pressure, cardiac output, heart rate and total peripheral resistance), thus reduce neurological impairment, and has been widely used to treat cerebrovascular diseases. In terms of neuroprotection, many studies have found that vinpocetine can inhibit the release of inflammatory

factors and the activation of microglia by inhibiting the NF-κB signaling pathway, thus playing a neuroprotective role. A multicenter, randomized controlled, evaluator-blind study on ischemic stroke patients with onset time of 4.5~48h showed that vinpocetine can inhibit the inflammatory response level in the area around the infarction and the inflammatory factor level in the peripheral blood, and can inhibit the expansion of the infarction volume, thereby improving clinical prognosis, relieving the cytotoxic effect induced by excitatory amino acids, inhibiting sodium iron and calcium ion channels, and enhancing the neuroprotective effect of adenosine. It interferes with atherosclerosis by reducing proliferation and migration of vascular smooth muscle, inhibiting rational remodeling of vascular diseases [158-160].

Edaravone is a free radical scavenger and antioxidant. Pre-clinical and clinical studies have shown that edaravone treatment can reduce the incidence of complications such as haemorrhagic transformation, progressive stroke, epilepsy, pulmonary infection and so on in patients with diabetic ischemic stroke [161-163].The subgroup analysis of the RESCUE-Japan Registry study found that edaravone combined with intravenous rt-PA or intravascular treatment group achieved a good prognosis proportion of neurological function in AIS patients with macroangiopathy within the treatment time window [164].

In a small preliminary rial, AIS patients were well tolerated with erythropoietin, which may improve the functional outcome for one month and reduce the occurrence of post-stroke complications. However, it has not been proved by other trials, and the

data failed to show an improvement in prognosis [165-167].

Ginkgolides mainly inhibit platelet aggregation and promote the recovery of nerve function by antagonizing the platelet activating factor (PAF) [168].A multicentre, randomized, double-blind, placebo-controlled clinical study of 949 patients with ischemic stroke within 72 hours is also underway to observe the effect of AIS combined with Ginkgolide Injection on neurological outcome [169].

Prostaglandin E1 (Alprostadil, PGE1) plays an important role in the treatment of ischemic stroke by reducing the generation of oxygen free radicals and the release of proteolytic enzymes, reducing the synthesis and release of TXA2, and protecting vascular endothelium [170].

A randomized controlled study on glycine showed that it was safe and effective for AIS patients [171].Several studies of N-methyl-D-aspartic acid receptor glycine site antagonist suggest good tolerance, but the application in AIS patient within 6h fails to improve prognosis [172-174].

Preliminary trials on lubeluzole showed that lubeluzole is safe [175], and can reduce mortality, but the following two larger-scale clinical trials found that lubeluzole is ineffective in reducing post-stroke mortality and improving prognosis [176-177]. NXY-059 is a free radical scavenger, and preliminary trials have showed good tolerance [178]. A study showed that it may reduce the disability rate and intracranial haemorrhage [179]. However, a key study to confirm the efficacy has not found any benefits [180].

Magnesium is an excitatory amino acid antagonist, calcium channel blocker and cerebral vasodilator. Although preliminary studies show that magnesium has good tolerance [181], and may improve prognosis [182], the results of subsequent larger-scale clinical trials are negative [183]. Several small-scale studies in China suggest that magnesium sulfate is effective for early treatment [184,185]. Considering the effect of application time on curative effect, a study preliminarily confirmed the safety and feasibility of pre-hospital ultra-early magnesium sulfate treatment [186]. A large-scale clinical trial showed that it is safe to start magnesium sulfate treatment before admission, and treatment is allowed to start within 2 hours after stroke occurs, however, it does not improve the 90-day disability outcome [187].

Several clinical trials on the efficacy of citicoline have failed to prove its efficacy on AIS [188-190]. However, a meta-analysis on the research level showed that citicoline has a net benefit in reducing the disability rate [191].The meta-analysis shows that if drug therapy is started within 24 hours after symptoms occur, patients with moderate to severe stroke may benefit [192].

Several trials on ganglioside (GM1) have shown that it cannot improve the prognosis [193,194]. A systematic review of these drugs [195] also failed to show benefits in treatment. However, a small-scale study in China have shown that argatroban combined with gangliosides could improve the short-term neurological deficit and 90 days activity of daily living in AIS patients (superior to the aspirin monotherapy or argatroban sequential aspirin treatment group) [196].

II. Hypothermia

Experimental and local hypoxic brain injury models suggest that hypothermia has neuroprotective effects. Deep hypothermia is often used to protect brain tissue in major operations.

An RCT was performed to compare the mortality and neurological prognosis of patients with cerebral hemisphere infarction between the mild hypothermia group and normal body temperature group, there was no statistical difference in mortality, but the mild hypothermia had a better neurological prognosis [197]. A study evaluating mild hypothermia therapy with surface cooling device after intravenous thrombolysis showed that mild hypothermia therapy was relatively safe and feasible despite some adverse events compared with normal body temperature [198]. The results of two studies on intravascular hypothermia therapy for patients after intravenous thrombolysis showed that hypothermia therapy was safe and feasible, but it had no obvious clinical benefits and can not reduce the incidence of pneumonia [199, 200]. The ReCCLAIMI Phase I study mainly evaluated the feasibility and safety of intravascular hypothermia immediately after arterial reperfusion therapy. Compared with patients with historical control, it is proved that hypothermia can prevent intracerebral haemorrhage (*OR*=0.09, 95% *CI:* 0.02-0.56, *P*< 0.01), and is safe and feasible [201]. A prospective cohort study compared the safety and prognosis of the mild hypothermia group and control group in AIS patients after successful revascularization. The results showed that the mild hypothermia group (*n*=39) had less cerebral oedema (*P*=0.001),

haemorrhagic transformation (P=0.016) and better outcomes (P=0.017) than the normothermia group (n=36). Conclusion: For patients with ischemic stroke, after successful recanalization, hypothermia therapy may reduce the risk of cerebral oedema and haemorrhagic transformation, and lead to improvement of clinical outcomes [202].

With regard to different cooling methods, a randomized trial compared the safety and cooling ability of intravascular cooling and surface cooling, showing that hypothermia therapy is feasible for patients under general anesthesia, the incidence of pneumonia in the hypothermia treatment group increases, and intravascular cooling has a faster induction period than surface cooling [203].

As far as cooling temperature is concerned, a multi-center RCT evaluated the feasibility and safety of surface cooling at different target temperatures in conscious patients with AIS. The conclusion is that in the conscious AIS patients, the surface cooling could reach 35.0℃, but could not reach 34.5℃ and 34.0℃, cooling was associated with increased risk of pneumonia. However, the study was terminated after 22 subjects were enrolled due to slow recruitment [204]. Two observational studies evaluated the safety and feasibility of moderate hypothermia and its potential to reduce intracranial pressure, and concluded that moderate hypothermia is feasible in patients with acute stroke, although it is related to several side effects. Most deaths occur during rewarming due to rebound of intracranial pressure [205, 206].

III. Hyperbaric oxygen

Although preclinical studies on acute cerebral ischemia show that hyperbaric oxygen therapy is usually relatively beneficial, in clinical trials, the efficacy of hyperbaric oxygen therapy for AIS is uncertain or shows that this measure does not improve the prognosis. A small sample RCT compared the functional outcomes of the hyperbaric oxygen treatment group and the control group in the early phase (2 weeks after onset) and the late phase (1 month after onset), the results showed that there was no significant difference in the early curative effect, but there was significant difference in the late curative effect, indicating that hyperbaric oxygen treatment may be effective for AIS patients [207]. Many small sample studies in China [208-209] and two meta analyses [210-211] have shown that hyperbaric oxygen or hyperbaric oxygen combined with drug therapy is beneficial to AIS patients, but due to its small sample size and relatively poor research quality, its conclusion cannot be used as effective evidence. In a review of 11 RCTs involving 705 AIS participants treated with hyperbaric oxygen, the results showed that there was no difference in 6-month mortality between the HBO treatment group and the control group (RR=0.97, 95% *CI:* 0.34-2.75, *P*=0.96). However, 4 of the 14 disability and functional outcome indicators showed that hyperbaric oxygen treatment had certain benefits. The conclusion is that there is no evidence that hyperbaric oxygen treatment can improve AIS outcomes, although clinical benefits cannot be excluded. In addition, due to different test methods, it is difficult to summarize and analyse the results other than the mortality rate [212]. Therefore, current research data do not support routine

applications of hyperbaric oxygen treatment for AIS.

Regarding hyperbaric oxygen treatment, most studies have proved that it is safe, but there are still some side effects. A review has mentioned that middle ear barotrauma is the most common complication, and other side effects include paranasal sinus/paranasal sinus barotrauma, dental barotrauma, pulmonary barotrauma, increased blood pressure, claustrophobia, and epileptic seizures [213]. A retrospective study involved 931 patients and underwent 23,328 times of hyperbaric oxygen therapy, mainly assessing the overall incidence of epilepsy and the risks under different treatment pressures. The results showed that the seizure rate was 1 seizure in 2121 treatments (about 5 seizures per 10000 treatments), and the higher the pressure, the more frequent the seizure. The conclusion is that hyperbaric oxygen treatment is related to the increased risk of epileptic seizure. The higher the pressure, the greater the risk. However, the study population was all patients treated with hyperbaric oxygen, not only the ischemic stroke patients [214].

Hyperbaric oxygen treatment is a recognized treatment method for cerebral air embolism related to compressed-air diving accidents, thus it is also the standard treatment for iatrogenic causes of gas embolism. A study retrospectively analysed the characteristics of 36 patients with cerebral gas embolism (CAGE) and the prognosis of hyperbaric oxygen treatment, which showed that a high proportion of CAGE patients who received hyperbaric oxygen treatment had good curative effect. The time from onset to hyperbaric oxygen treatment ≤ 6h can increase the possibility of

favourable outcome, while CT/MRI scan before hyperbaric oxygen treatment found that infarction/oedema had reduced the possibility of favourable outcome [215]. Stroke is a rare but serious complication in cardiac surgery. In most cases, cerebral gas embolism is the possible cause. A study on AIS hyperbaric oxygen therapy after cardiac surgery shows that hyperbaric oxygen treatment is related to significant improvement of acute neurological impairment caused by ischemic stroke after cardiac surgery. Although gas embolism is the most likely cause of stroke in this type of patients, other potential pathological mechanisms cannot be excluded and need further evaluation through random studies [216].

IV. Mechanical blood flow increase method

The mechanical method to increase cerebral perfusion is a method to improve cerebral blood flow through the Will circle and pia mater vessels, rather than through the action of vasoconstrictors. In 1997, a study led by Applebaum et al [217] aimed to evaluate the effect of external counterpulsation (ECP) on cerebral blood flow and renal blood flow. The results show that this non-invasive treatment may be helpful to support patients with cerebral perfusion and renal perfusion reduction. In 2008, Han[218] also found that ECP is beneficial to patients with macrovascular ischemic stroke. In recent years, other research results have proved that ECP is safe and feasible, applicable to AIS, and it is related to the improvement of the NIHSS score regardless of the pressure used [219]. However, some studies have drawn different conclusions, and believed that NeuroFlo therapy has nothing to do with the clinical

outcome of AIS [220]. After that, Hammer et al[221]pointed out that it may be safe and feasible to use NeuroFlo catheter for partial aortic occlusion within 8-24 hours after onset of symptoms when evaluating the safety and feasibility of NeuroFlo in patients with ischemic stroke within 8-24 hours after onset.

Recommendations

[1] Evidence in basic and preclinical studies suggests that neurovascular protection therapy may be beneficial, but has not been proved in clinical studies to improve prognosis of AIS patients and reduce recurrence. More clinical research is still needed, some related researches are also in progress currently (Class IIb, Level of Evidence B).

[2] The efficacy of induced hypothermia in patients with ischemic stroke is unclear and further studies are needed. Most studies have found that induced hypothermia was a risk for infection, including pneumonia. Induced hypothermia should be administered only in clinical trials (Class IIb, Level of Evidence B).

[3] Hyperbaric oxygen therapy is not recommended for AIS patients unless it is caused by air embolism. Hyperbaric oxygen therapy is related to claustrophobia, middle ear barotrauma and the increased risk of seizures (Class III, Level of Evidence B).

[4] Mechanical augmentation of blood flow to treat AIS patients has not been

perfected, curative effect is not sure, and only can be used in clinical trials (Class IIb, Level of Evidence B).

V. Induced hypertension

Elevated systemic blood pressure in patients with acute ischemic stroke can increase the local cerebral blood flow, and increase the local cerebral blood flow through lateral branches and arterioles. Many research results show that induced hypertension treatment in the acute phase may improve neurological impairment in AIS patients [222]. However, Koenig et al reviewed 100 AIS patients, of which 46 were treated with induced hypertension (IH group) and 54 were treated with conventional therapy (ST group). The results showed that the NIHSS scores of the two groups of patients were similar in hospital and at discharge, and the recurrence rate of vascular events had no significant difference between the two groups.

VI. Blood volume expansion and haemodilution

Since the end of 1960s, there has been continuous research on the efficacy of haemodilution therapy for acute stroke patients, but the research conclusions are contradictory [223-227]. In 2014, a meta-analysis involving 21 trials and 4,174 samples showed that there is still no clear evidence to prove that haemodilution therapy is beneficial to the prognosis of AIS [228]. In 2017, Joseph et al[229] analysed the ALIAS II data to assess whether the extent of plasma volume expansion affects neurological function recovery in AIS patients. The results confirmed that plasma volume

expansion is related to the poor prognosis of neurological function.

VII. Near infrared laser therapy

The randomized controlled study NEST-1 preliminarily confirmed the safety and efficacy of infrared laser therapy in the treatment of ischemic stroke within 24 hours after onset [230].The NEST-2 study further confirmed its safety, but its effectiveness was not significant enough [267]. A summary analysis of the results of NEST-1 and NEST-2 indicates that there is a statistical difference in the 90d mRS scores, of which moderate stroke has better response to treatment [231].However, in the NEST-2 study, the infarct volume of patients was evaluated before and after treatment. The results showed that laser treatment had nothing to do with the overall or cortical infarct volume reduction measured by subacute CT [269]. The follow-up Phase III trial was terminated due to no significant difference in mid-term efficacy analysis. The conclusion was that transcranial laser therapy had no measurable neuroprotective effect within 24 hours after AIS onset [234-235].

VIII. Albumin

In many observational studies, albumin reduction is associated with high mortality and disability in patients with ischemic stroke [236-237]. Relevant studies have confirmed that albumin therapy has neuroprotective effect in the acute phase [238-240]. The ALIAS study evaluated the efficacy of 6 different doses (0.34-2.05 g/kg) of albumin in the treatment of AIS. The results showed that the good clinical outcome (mRS score of 0-1 or NIHSS score of 0-3) rate in the higher dose albumin treatment

group was 81% higher than that in the lower dose albumin treatment group. The number of subjects receiving higher dose albumin in the intravenous rt-PA treatment group who achieved good clinical outcomes was 3 times higher than that in the lower dose group. Albumin and intravenous rt-PA may have synergistic effect in AIS treatment [241-242]. However, there are also corresponding research results that confirm that there is no obvious correlation between the two or that albumin therapy has a correlation with poor prognosis of patients [243-244]. In 2016, Martin et al. conducted a joint analysis of the ALIAS Part I and Part II trials. The results showed that there was no statistical difference in the 90-day disability rate between the two groups [245]. In 2018, Khatri et al analysed 1275 patients in the ALIAS trial to explore the neuroprotective effect of albumin on AIS patients. The results showed that for patients with large-area cardiogenic cerebral embolism (NIHSS score ≥ 15), high-dose albumin therapy started within 2 hours of onset had a trend of obvious benefits, indicating that certain types of stroke patients might benefit from albumin therapy. However, further clinical trials are still needed to classify patients according to the severity of NIHSS, so that treatment can be stratified to further evaluate the clinical effects of albumin treatment [246].

Recommendations

[1] Effectiveness of induced hypertension treatment in AIS patients is not clear, it can only be used in the study of clinical research (Class IIb, Level of Evidence B).

[2] It is not recommended for routine use of blood volume expansion or haemodilution therapy in AIS patients (Class III, Level of Evidence A).

[3] At present, there is no evidence that transcranial near infrared laser therapy for ischemic stroke is beneficial, therefore using transcranial near infrared laser treatment in ischemic stroke is not recommended (Class IIb, Level of Evidence B).

[4] The routine use of high-dose albumin therapy in patients with AIS is not recommended (Class III, Level of Evidence A).

Section 6 Routine support treatment and complication management for acute ischemic cerebrovascular disease

I. General supportive treatment

(I) Airway, ventilation support and supplementary oxygen supply

Oxygen deficiency often occurs after stroke [247-248]. The common causes of hypoxia include incomplete airway obstruction, hypoventilation, aspiration, atelectasis and pneumonia. Patients with decreased consciousness caused by brainstem dysfunction increase the risk of airway damage due to oropharyngeal activity damage and loss of protective reflex [249-250]. A recent RCT suggests that for acute stroke patients without hypoxemia, preventive low-dose oxygen supply cannot reduce the 3-month mortality and disability rate [251]. In addition, another cohort study [252] and 5 RCTs[253-257] also suggest that supplementary oxygen supply to patients with acute stroke has no definite benefits. According to these data, mild to moderate stroke patients without hypoxia do not need emergency routine supplementary oxygen supply. Supplementary oxygen supply for patients with severe stroke may be beneficial, although it has not been confirmed by the current data. Further research in this field is recommended [257].According to the data from the review (these data are mainly about patients recovering from cardiac arrest), the AHA guidelines on acute cardiovascular therapy for patients recovering from stroke and cardiac arrest recommend oxygen supply to patients with hypoxemia to maintain a blood oxygen saturation level of > 94% [294]. When there are indications for oxygen therapy, it is reasonable to adopt the least

invasive method to achieve normal oxygen concentration as much as possible. Effective methods include nasal catheter, biphasic positive airway pressure ventilation, continuous positive airway pressure ventilation or endotracheal intubation mechanical ventilation. At present, there is no clinical trial that evaluates the effectiveness of tracheal intubation in the management over patients with severe stroke. It is generally believed that tracheal intubation and mechanical ventilation should be implemented when the airway is threatened. Evidence shows that early prevention of aspiration can reduce the occurrence of pneumonia [258], and airway protection may be an important method for some patients. Tracheal intubation and mechanical ventilation are also helpful to reduce ICP elevation or malignant brain oedema after stroke [259-260].Tracheal intubation will affect the prognosis, although a few patients may obtain satisfactory prognosis [261]. However, the overall prognosis of stroke patients with tracheal intubation is poor, and the mortality rate within 30 days after stroke reaches 50% [262-264].

Recommendations

[1] Airway support and ventilator assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway (Class I, Level of Evidence C).

[2] Supplemental oxygen should be provided to maintain oxygen

saturation >94%. (Class I, Level of Evidence C).

[3] Supplemental oxygen is not recommended in nonhypoxic AIS patients (Class III, Level of Evidence B).

(II) Body temperature

About 1/3 of stroke inpatients have fever (body temperature > 37.6℃) in the early phase after onset [265-266].Fever may be secondary to stroke causes, such as infective endocarditis, or may be caused by stroke complications, such as pneumonia, urinary tract infection, UTI), or sepsis. Fever is related to the poor prognosis of neurological function in AIS patients, and maintaining the normal body temperature or decreasing the acute elevated body temperature may improve the prognosis of stroke patients [266].Measures to achieve the normal body temperature or prevent fever include drugs and physical intervention.

A large-scale randomized, double-blind, placebo-controlled trial evaluated whether early acetaminophen (acetaminophen) treatment can improve functional prognosis by lowering body temperature and preventing fever. The results showed that there was no statistical difference between the two groups. The post-event analysis showed that the treatment was beneficial to patients with baseline temperature of 37-39 C. The average hypothermia of patients in the treatment group was 0.26 ℃ (95% *CI:* 0.18-0.31) 24 hours after starting the treatment, which was lower than that in the control group. [267]. Another analysis showed that stroke patients with elevated body

temperature 24 hours after admission had worse prognosis. The risk of adverse outcome (*OR*=1.3, 95% *CI:* 1.05-1.63) and death (*OR*=1.51, 95% *CI:* 1.15-1.98) increases for every 1 ℃ rise in body temperature [268]. A recent retrospective cohort study included 9,366 AIS patients from intensive care units in Australia, New Zealand and the United Kingdom from 2005 to 2013. The results showed that patients with temperature peaks < 37℃ and > 39℃ within 24 hours after onset had an increased risk of death during hospitalization compared with patients with normal body temperature [269].

Hypothermia therapy is a promising neuroprotective strategy, but its benefits to AIS patients have not been confirmed. Most studies have shown that hypothermia induction is related to the increased risk of infection including pneumonia [194-195, 204, 270].Hypothermia therapy should only be used in clinical trials.

Recommendations

[1] Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Class I, Level of Evidence C).

[2] The benefit of induced hypothermia for treating patients with ischemic stroke is not well established. Hypothermia should be offered only in the ongoing clinical trials (Class IIb, Level of Evidence B).

(III) Nutrition and fluid infusion

Dehydration or malnutrition may delay recovery, so it is very important to maintain nutrition. Assessment of fluid and nutritional status after stroke should be emphasized, and fluid infusion and nutritional support should be given when necessary [271-272]. FOOD (Feed or Ordinary Diet; Phase I-III) results show that supplementary diet is associated with a 0.7% reduction in absolute risk of death, early tube feeding (within 7 days after admission) is associated with a 5.8% reduction in absolute risk of death and a 1.2% reduction in the incidence of death or poor prognosis. Compared with percutaneous endoscopic gastrostomy tube feeding, nasal feeding is associated with a 1.0% increase in absolute risk of death and a 7.8% increase in the incidence of death or poor prognosis [273]. The research conclusion suggests that enteral nutrition should be started within 7 days after admission of stroke patients. A 2012 Cochrane review included 6779 patients in 33 RCT studies, and evaluated the efficacy of dysphagia intervention treatment, feeding strategy and time [early phase (within 7 days) vs. late phase], fluid infusion and nutritional supplement for patients with acute and subacute stroke [274]. The conclusion is that there is no obvious difference in the fatality, mortality and disability rate between percutaneous endoscopic gastrostomy tube feeding and nasal feeding. Although the data are not enough to determine which of the two feeding methods are better, percutaneous endoscopic gastrostomy tube feeding has fewer treatment failures (P=0.007), less gastrointestinal bleeding (P=0.007) and higher feeding costs (P< 0.00001).

Limited research results show that the implementation of intensive oral hygiene programs may reduce the risk of aspiration pneumonia. Sorensen et al [275] analysed the relevant intervention measures for patients with acute stroke. After comparing the intervention group that adopted standardized dysphagia screening, diet and standardized chlorhexidine antibacterial oral hygiene program with the historical control group that did not systematically screen dysphagia within 24 hours and did not systematically receive chlorhexidine antibacterial oral hygiene program, it was found that the former standardized intervention measures could reduce the incidence of pneumonia (7% vs. 28%). Specifically, the efficacy of the standardized oral hygiene program in the intervention group cannot be separated from standardized dysphagia screening and diet. In addition, due to the historical nature of the control group, there may be changes in nursing between patients in the historical control group and the intervention group, which may affect the risk of occurrence of pneumonia. After a Cochrane review included three studies, the analysis found that the incidence of pneumonia in the intervention group of oral care combined with disinfection gel was lower than that of oral care combined with placebo gel (P=0.03) [276]. Wagner et al[277]compared the risk of pneumonia before and after systematic oral health care for stroke inpatients. Compared with the control group, the uncorrected incidence of hospital-acquired pneumonia in the intervention group with oral health care was lower (14% vs. 10.33%). P=0.022), and the uncorrected OR was 0.68 (95% *CI:* 0.48-0.95, P=0.022). After correction of confounding factors, the OR value of hospital acquired

pneumonia in the intervention group was still significantly lower, and was 0.71 (95% *CI:* 0.51-0.98, *P*=0.041).

Recommendations

[1] Enteral diet should be started within 7 days of admission after an AIS (Class I, Level of Evidence B).

[2] For patients with dysphagia, it is reasonable to initially use nasogastric tube 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) (Class IIa, Level of Evidence C).

[3] Nutritional supplements are reasonable to consider for patients who are malnourished or at risk of malnourishment (Class IIa, Level of Evidence B).

[4] Implementing oral hygiene protocols to reduce the risk of pneumonia after stroke may be reasonable (Class IIb, Level of Evidence B).

(IV) Infection prevention

For stroke patients with limited mobility and cough, pneumonia is not only the most common complication, but also one of the important causes of death after stroke [278-282]. Aslanyan et al [318] found that pneumonia was associated with increased risk of death (HR=2.2, 95% *CI:* 1.5-3.3) or adverse outcomes (*OR*=3.8, 95% *CI:* 2.2-6.7).

Stroke-related pneumonia can increase the length of hospitalization, mortality rate and hospitalization expenses[283]. Limited mobility and atelectasis can lead to pneumonia. Early activities and good lung care are helpful for preventing pneumonia [284]. Preventive measures for tracheal intubated patients include semi-horizontal ventilation, airway position, sputum aspiration, early activities, and shortening the time of intubation when possible [322].Treatment of nausea and vomiting can also reduce the risk of aspiration pneumonia. Exercise and deep breathing help reduce the occurrence of atelectasis. For post-stroke fever, physicians should actively search for signs of pneumonia, and appropriate antibiotic treatment should be given in time. Some studies have found that early preventive administration of levofloxacin after stroke has failed to reduce the risk of pneumonia or other infections [285].

Urinary tract infection is common after stroke, which can occur in 15%-60% of patients. Urinary tract infection is not only an independent predictor of poor outcomes, but is also is a potential complication that can lead to bacteremia or septicemia [280, 286-289]. Patients with stroke should have routine urine tests whenever fever occurs in order to clarify evidence of infection. Some patients have a high risk of urinary incontinence, especially those with severe disabilities [290]. Catheter indwelling should be avoided as much as possible, but indwelling may be necessary in acute stroke, and the catheter should be removed as soon as the patient's condition is stable. Intermittent catheterization can reduce the risk of infection. External catheter, paper diaper and intermittent catheter can be used to replace indwelling

catheter. If a patient's level of consciousness changes and it is determined that there is no other cause leading to deterioration of neurological function, the presence of urinary tract infection should be evaluated. If urinary tract infection is suspected, routine urinalysis and urine culture should be performed [280-281,291]. Urine acidification can reduce the risk of infection, and anticholinergic drugs may help restore bladder function. Although preventive antibiotics are not routinely used, antibiotics should be reasonably applied when the evidence of urinary tract infection is clear.

Recommendations

[1] Routine use of prophylactic antibiotics has not been shown to be beneficial (Class III, Level of Evidence B).

[2] Routine placement of indwelling bladder catheters should not be performed because of the associated risk of catheter-associated urinary tract infections (Class III, Level of Evidence C).

(V) Prevention of lower limb venous thrombus and pulmonary embolism

CLOTS (Clots in Legs or Stockings After Stroke) 3 is a multi-centre trial involving 2,867 patients in 94 centres in the UK, which compared the preventive effects of conventional treatment with or without intermittent pneumatic compression (IPC) on venous thromboembolism in stroke patients with limited mobility. The study included

acute stroke patients within 3 days of onset and could not independently have bowel movements. Conventional treatment is defined as possible application of aspirin, fluid infusion and elastic stockings for non-haemorrhagic stroke. 31% of the patients used prophylactic, full dose or low molecular heparin, but these patients were evenly distributed between the two groups. The survival rate of the patients in the IPC group was significantly improved at 6 months (HR=0.86, 95% *CI:* 0.73-0.99, *P*=0.042), but the disability rate was not improved. Skin damage was more common in the IPC group (3.1% vs. 1.4%, *P*=0.002). Contraindications for IPC include local lesions of lower limbs such as dermatitis, gangrene, severe oedema, venous blood stasis, severe peripheral vascular disease, postoperative vein ligation, skin transplantation, or swelling of lower limbs and other signs indicating deep venous thrombosis (DVT) [292]. A meta-analysis included in the study and 2 other small-scale trials reconfirmed the above results [293].

In a recent systematic meta-analysis on prophylactic drug intervention of venous thrombosis in AIS patients included 1 large sample trial (*n*=14578) and 4 small sample trials on unfractionated heparin, 8 small sample trials on low molecular heparin or heparinoid and 1 trial on heparinoid[293]. Preventive anticoagulants had no significant effect on mortality and functional status at final follow-up. Symptomatic pulmonary embolism (*OR*=0.69, 95% *CI:* 0.49-0.98) and DVT (mostly asymptomatic) (*OR*=0.21, 95% *CI:* 0.15-0.29) were significantly reduced. Symptomatic intracranial haemorrhage (*OR*=1.68, 95% *CI:* 1.11-2.55) and

symptomatic extracranial haemorrhage (*OR*=1.65, 95% *CI:* 1.0-2.75) increased significantly. It is possible that the benefits of reduced risk of venous thromboembolism in some patients are sufficient to offset the increased risk of intracranial and extracranial haemorrhage, but there is no prediction tool to determine this part of patients [293-295].

A recent systematic meta-analysis compared the use of low molecular heparin/heparan and unfractionated heparin to prevent venous thromboembolism in AIS patients, including 1 large sample trial (n = 1762) and 2 small sample trials comparing low molecular heparin and unfractionated heparin, and 4 small sample trials comparing unfractionated heparin and unfractionated heparin. Compared with unfractionated heparin, low molecular heparin/heparan had no obvious effect on death or disability. Low molecular heparin/heparan could significantly reduce risk of DVT (mostly asymptomatic) (*OR*=0.55, 95% *CI:* 0.44-0.70), while the risk of severe extracranial haemorrhage increased (*OR*=3.79, 95% *CI:* 1.30-11.03). Low molecular heparin can be injected once a day, so nursing is more convenient and patients are more comfortable. It should be noted that for elderly patients with renal impairment, the use of low molecular heparin may increase the risk of bleeding and increase the medical expenses.

Recommendations

[1] In immobile stroke patients without contraindications, intermittent

pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT) (Class I, Level of Evidence B).

[2] The benefit of prophylactic-dose subcutaneous heparin (UFH or LMWH) in immobile patients with AIS is not well established (Class IIb, Level of Evidence A).

[3] When prophylactic anticoagulation is used, the benefit of prophylactic-dose LMWH over prophylactic-dose UFH is uncertain (Class IIb, Level of Evidence B)

[4] In ischemic stroke, elastic compression stockings should not be used (Class III, Level of Evidence B).

(VI) Early rehabilitation

When a patient's condition is stable, he or she should start physical activities such as sitting, standing and walking as soon as possible. When the condition of bedridden patients permits, attention should be paid to the placement of normal limbs. Attention should be paid to language, sports, psychology and other aspects of rehabilitation training in order to restore the ability of daily living as much as possible. The AVERT (A Very Early Rehabilitation Trial) study randomly assigned 2104 patients with acute stroke (1: 1) and compared the high-intensity, ultra-early activity programs with the standard treatment activity programs [296]. However, the findings show that compared

with the conventional treatment group, the high intensity and ultra-early activity group had less favourable prognosis (46% vs. 50%), higher mortality (8% vs. 7%), and more non-lethal serious adverse events (20% vs. 19%). Therefore, the early activities should be moderate, so as to avoid over early resumption of activities.

Recommendations

[1] It is recommended that early rehabilitation for hospitalized stroke patients be provided in environments with organized, multidisciplinary stroke care (Class I, Level of Evidence A)

[2] It is recommended that stroke survivors receive rehabilitation at an intensity commensurate with anticipated benefit and tolerance (Class I, Level of Evidence B).

[3] High-dose, very early mobilization within 24 hours of stroke onset should not be performed because it can reduce the odds of a favourable outcome at 3 months (Class III, Level of Evidence B).

[4] It is recommended that all individuals with stroke be provided a formal assessment of their activities of daily living and instrumental activities of daily living, communication abilities, and functional mobility before discharge from acute care hospitalization and the findings be incorporated into the care transition and the discharge planning process (Class I, Level of Evidence B).

[5] A functional assessment by a clinician with expertise in rehabilitation is recommended for patients with an acute stroke with residual functional deficits (Class I, Level of Evidence C).

II. Management of nervous system complications

(I) Cerebral oedema and signs of mass lesions

1. Medical therapy Cerebral oedema can be seen in all types of cerebral infarction, especially massive cerebral infarction. Various drug interventions are suggested to alleviate the development of oedema, such as limiting liquid intake to reduce hypotonic liquid, avoiding excessive glucose intake, improving hypoxemia and hypercapnia, and inducing hypothermia therapy. Antihypertensive drugs, especially those that can cause cerebrovascular contraction, should be avoided. Raising the head of the bed by 20°-30° is helpful for venous drainage. The goal of these interventions is to reduce or alleviate oedema formation before intracranial pressure increases significantly due to cerebral oedema. Standardized intracranial pressure management should be started when intracranial pressure increases due to cerebral oedema [335]. The intracranial pressure management scheme is similar to treatment for traumatic brain injury and spontaneous cerebral haemorrhage, including hyperventilation, hypertonic saline, osmotic diuretics, ventricular drainage of cerebrospinal fluid, and surgical decompression [297-298]. At present, there is no evidence that hyperventilation, conventional or high-dose steroid drugs, diuretics, mannitol/glycerol fructose or other

measures to reduce intracranial pressure can improve the prognosis of patients with ischemic cerebral oedema. Mannitol (0.25-0.5g/kg) can be given intravenously every 6h for more than 20min to reduce intracranial pressure, and the maximum conventional dose is 2g/kg. Koenig et al [299]'s preliminary study found that hypertonic saline can rapidly reduce intracranial pressure in patients with clinical tentorial herniation caused by various supratentorial lesions (including ischemic and haemorrhagic stroke), and the results of this stroke-related study supplement and support the data for previous studies on traumatic brain injury. Hyperventilation is a very effective treatment for rapidly improving cerebral oedema, but it takes effect by inducing cerebral vasoconstriction. If persistent hypocapnia occurs, it can aggravate ischemia [300]. Therefore, hyperventilation should be induced as soon as possible to avoid excessive hypocapnia (< 30mmHg). At present, the evidence for the treatment of AIS with hypothermia or barbiturates is still limited. The existing data only come from studies of small sample size and unclear intervention time. A recent meta-analysis involving 6 RCTs showed that hypothermia had no effect on stroke outcome [301]. Further related studies are recommended. Although active drug management has been given, the mortality rate of patients with intracranial hypertension is still as high as 50%-70%. Therefore, these interventions should be considered as temporary measures to extend the time window before final treatment.

2. Surgical treatment Cerebral hemispheric infarction is often caused by occlusion of proximal large vessels and is associated with massive cerebral infarction that often

involves upper and lower brain tissues of lateral fissure [302-304]. Imaging studies showed that in early CT, low density lesions in more than 2/3 of the middle cerebral artery area [302], perfusion restriction [305-306] or lack of perfusion [307], all indicate that the risk of delayed cerebral hernia is increased. Clinical deterioration often progresses rapidly. When accompanied with brainstem compression, the rapid dysfunction of the upper part of the brainstem may first lead to deterioration of the consciousness level [308-309]. Even if the maximum degree of drug administration had been given, the death rate of patients with consciousness deterioration is still 50%-70% [310]. Brain stem compression is often accompanied by secondary effects of frontal lobe and occipital lobe, which may be caused by dural structure compression by anterior and posterior cerebral arteries [311-312]. The secondary infarction caused by this greatly limits the potential possibility of clinical rehabilitation and even survival.

Cerebral oedema in patients with supratentorial massive cerebral infarction can lead to serious and even life-threatening complications. Although less severe brain oedema can be managed by drug treatment, surgical treatment may be the only effective choice for patients with severe brain oedema. In this case, timely decompressive craniectomy can reduce the mortality rate [313]. Summary results of several RCTs showed that decompressive craniectomy can significantly reduce mortality within 48 hours after onset of malignant middle cerebral artery infarction in patients under 60 years old, and the absolute risk of mortality at 12 months can be reduced by 50% (95% *CI:* 34-66) [313]. The study II of "Decompressive Surgery for the Treatment of

Malignant Infarction of the Middle Cerebral Artery" (DESTINY) showed that decompressive craniectomy can reduce the mortality rate by about 50% (76% in non-operative group and 42% in operative group) within 48 hours after stroke onset for patients with malignant infarction of middle cerebral artery who are aged > 60 years [314-320]. However, the functional outcome of these elderly patients seemed to be worse than that of patients aged < 60 years. None of the patients in the two groups achieved self-care within 12 months (mRS score ≤ 2).

Ventricle drainage is recognized as an effective treatment for acute obstructive hydrocephalus, and often can effectively relieve the symptoms of patients with acute ischemic stroke [321-322]. Therefore, ventricular drainage is the reasonable first choice for patients with cerebellar ischemic stroke with obstructive hydrocephalus. If drainage of cerebrospinal fluid through ventricle drainage fails to improve neurological function, suboccipital decompressive craniectomy should be performed [321-323].Although simple ventricular drainage has the risk of tentorial notch hernia, if cerebellar infarction causes significant brain oedema or mass effect, the risk can be minimized by conservative cerebrospinal fluid drainage or suboccipital decompressive craniectomy. Research data support cerebellar decompressive craniectomy in patients with mass effect in acute ischemic minor stroke [321-323]. For patients with cerebellar infarction, when it is impossible to treat obstructive hydrocephalus with medication or ventricular drainage and neurological deterioration due to cerebral oedema occurs, cerebellar decompressive craniectomy can be used for

intervention treatment [321-322].

Please refer to Figure 5 for a summary of the treatment process of cerebral oedema/intracranial hypertension.

Recommendations

[1] Patients with major infarctions are at high risk developing brain edema and intracranial hypertension. Transfer of patients to intensive care unit should be considered. Measures to lessen the risk of edema and close monitoring of patients for signs of neurological worsening during the first days after stroke are recommended (Class I, Level of Evidence C).

[2] In patients ≤60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is reasonable (Class IIa, Level of Evidence A).

[3] In patients >60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion may be considered (Class IIB, Level of Evidence B).

[4] Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness attributed to brain swelling as selection criteria (Class IIa, Level of Evidence A).

[5] Ventriculostomy is recommended in the treatment of obstructive

hydrocephalus after a cerebellar infarct. Concomitant or subsequent decompressive craniectomy may or may not be necessary on the basis of factors such as infarct size, neurological condition, degree of brainstem compression, and effectiveness of medical management (Class I, Level of Evidence C).

[6] Decompressive suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarction causing neurological deterioration from brainstem compression despite maximal medical therapy. When deemed safe and indicated, obstructive hydrocephalus should be treated concurrently with ventriculostomy (Class I, Level of Evidence B).

[7] Use of salvage osmotic therapy for patients with clinical deterioration from occupying signs associated with major supratentorial infarction or cerebellar infarction is reasonable (Class IIa, Level of Evidence C).

[8] 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 (Class IIa, Level of Evidence C).

[9] Hypothermia or barbiturates in the setting of ischemic cerebral or cerebellar swelling is not recommended (Class III, Level of Evidence B).

[10] Because of a lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) should not be administered for the treatment of cerebral edema and increased intracranial pressure (Class III, Level of Evidence A).

(II) Haemorrhagic transformation

Ischemic stroke is often accompanied by petechial haemorrhage, patients have not received vascular recanalization treatment and has no deterioration of neurological function related to haemorrhage [324-325]. However, symptomatic haemorrhage occurs in 5%-6% of patients treated with rt-PA intravenous thrombolysis, intravascular recanalization and anticoagulant drugs [326-329].Haemorrhagic transformation can also occur in patients who have not undergone vascular recanalization therapy, especially in patients with massive infarction, older age, cardiogenic embolism and other factors. Studies show that the prognosis of asymptomatic haemorrhagic transformation patients is not different from that of patients without haemorrhagic transformation, and there is still no research evidence for its treatment. Therefore, there is currently no recommended special treatment for asymptomatic haemorrhagic transformation patients. Symptoms and signs of symptomatic haemorrhagic transformation are similar to spontaneous cerebral haemorrhage, such as deterioration of nervous system function, mental state decline, headache, increase of blood pressure and pulse, and vomiting [330]. Therefore, early clinical judgment, early warning and adjustment of treatment plan are of great significance to the prognosis of these patients. At present, there are many predictive scoring models for haemorrhagic transformation risks, which can help guide the expectations of patients and their families, and may indicate the required medical monitoring intensity of individual patients after intravenous

thrombolytic therapy. Treatment of haemorrhagic transformation requires complex comprehensive management, including blood pressure management, reversal of coagulation dysfunction and management of complications such as intracranial hypertension [331]. At present, there is also a lack of high-quality research evidence on symptomatic haemorrhagic transformation therapy and when to reuse antithrombotic drugs (anticoagulant and antiplatelet), so there is no unified standardized therapeutic regimen. A large number of observational studies show that the initiation or continuation of antithrombotic therapy for patients with haemorrhagic transformation after AIS will not lead to deterioration of the disease condition, provided that assessment of the clinical indications, benefits and risks is ensured [332-333].

See Supplemental Table 9 for specific types of haemorrhagic transformation in ischemic stroke.

Please refer to Figure 6 for details of the treatment process of haemorrhagic transformation of acute ischemic stroke.

Recommendations

[1] Symptomatic haemorrhagic transformation: stop using anti-thrombotic (antiplatelet, anti-coagulation) (Class I, Level of Evidence C); For haemorrhage management associated with anticoagulation and thrombolysis, refer to cerebral haemorrhage treatment guidelines.

[2] For AIS patients with haemorrhagic transformation, starting or continuing

antiplatelet or anticoagulant therapy should only be decided according to the specific clinical conditions and potential indications (Class IIb, Level of Evidence B).

(III) Epilepsy after stroke

The incidence rate of epilepsy after ischemic stroke is quite different in various literature reports, but the incidence rate in most cases is less than 10% [334-335]. Some reports show that the incidence of epilepsy in patients with haemorrhagic transformation of ischemic stroke is significantly increased [336]. The incidence of recurrent and delayed epilepsy in previous reports is also quite different [337-338]. The applicable data on the effectiveness of anti-epileptic drugs for stroke patients are limited, and the current recommendation is based on the established management over neurological diseases complicated with epilepsy. At present, there is no research evidence showing that preventive antiepileptic therapy can be benificial after ischemic stroke, and there is only a small amount of relevant information about the indications of long-term use of antiepileptic drugs after epileptic seizure.

See Figure 7 for details of the treatment process of the first epileptic seizure within 24 hours after stroke onset.

Recommendations

[1] Recurrent seizures after stroke should be treated in a manner similar to when

they occur with other acute neurological conditions, and anti-seizure drugs should be selected based upon specific patient characteristics (Class I, Level of Evidence C).

[2] Prophylactic use of anti-seizure drugs is not recommended (Class III, Level of Evidence B).

Section 7 Early evaluation and diagnosis of aetiology and pathogenesis of ischemic cerebrovascular disease

I. Recommended examination and evaluation to be performed

(I) Imaging examination of brain and blood vessels

1. Brain parenchyma imaging

(1) Noncontrast CT

1) According to a number of large sample clinical observational studies, plain CT is an optimal cost-effective imaging method, which can detect intracranial haemorrhage and avoid antithrombotic treatment in these patients [339-340]. MRI-DWI is more sensitive than noncontrast CT for detecting AIS, especially for posterior circulation ischemic stroke[341-343]. In many patients, the diagnosis of ischemic stroke can be made on the basis of the clinical symptoms and noncontrast CT excluding intracranial haemorrhage [344]. MRI-DWI can provide certain information for the follow-up intravascular treatment in patients with suspected diagnosis of ischemic stroke or unclear location of responsible vessel areas.

2) A number of large clinical trials, including NINDS, ECASS II, IST-3 and a meta-analysis in 2016, showed that there was no statistically significant modification of the effect of rt-PA by the following findings on baseline CT including hypodensity in brain parenchyma, hyperdense middle cerebral artery sign, semi-quantitative score ASPECTS or leukoaraiosis [345-351].

Recommendations

[1] All patients admitted to acute care hospital for ischemic stroke should be evaluated by cranial imaging. For the majority of patients, the head CT scan is the first selection (Class I, Level of Evidence B).

[2] Early ischemic signs or leukoaraiosis showed on CT cannot be an absolute exclusion standard for IV thrombolysis (Class III, Level of Evidence B).

(2) MRI

Two meta-analyses in 2016 have shown that cerebral microbleeds (CMB) are risk factors for symptomatic intracranial haemorrhage(sICH) after thrombolysis (*OR*=2.18, 95% *CI:* 1.12-4.22, *P*=0.021; *OR*=2.36，95% *CI:* 1.21~4.61，*P*=0.01). However, sICH in patients with baseline CMBs is not more common (6.1%, 6.5%) than in the NINDS rtPA trial (6.4%) [77, 352]. At the same time, both meta-analyses include observational studies.

To date, no relevant RCT have been conducted to confirm the effect of baseline CMB on the treatment efficacy and clinical outcome of thrombolysis. Therefore, according to the existing evidence, CMB on baseline MRI can not affect the clinical decision about intravenous thrombolysis.

Recommendations

Routine use of MRI to identify intracranial microhemorrhage, which can affect

decisions to IV thrombolysis, is not recommended (Class III, Level of Evidence B).

2. Intracranial and extracranial angiography

A systematic review of 36 studies in 2018 concluded that currently there is no prediction instruments with high sensitivity and specificity (including NIHSS, CPSSS, LAMS, RACE) to diagnose large vessel occlusion. The study believed that the NIHSS score is still the best tool to evaluate the disease condition in emergency, but there is no strong evidence for pre-hospital identification and transfer of patients with large artery occlusion [353].

Many observational studies which inculde more than 100 AIS patient suggest that the risk of contrast-induced nephropathy secondary to CTA imaging is relatively low, particularly in patients without a history of renal impairment. Therefore, there is no need to delay starting treatment in order to wait for creatinine results [354-356].

Knowledge of extracranial vessel anatomy and presence of dissections, stenoses or occlusions may assist in evaluating the risk of endovascular treatment and making treatment decision.

Recommendations

[1] Patients with suspicious endovascular treatment should complete the non-invasive vascular evaluation as soon as possible, but should pay attention to

avoid delaying thrombolysis (Class I, Level of Evidence B).

[2] Patients with suspected arterial occlusion and without previous renal impairment can conduct the head and neck CTA inspection directly, in order to avoid delay in treatment time in order to wait for creatinine to be resulted (Class I, Level of Evidence B).

[3] For patients who may need intravascular therapy, completing the evaluation of extracranial vessels including extracranial internal carotid artery and vertebral artery is helpful for guiding the treatment options (Class IIa, Level of Evidence C).

(2) Cardiac examination (structure, rhythm, function and ECG activity)

1. Cardiac structure evaluation Besides atrial fibrillation (AF), cardiac structure and function are associated with higher risk of stroke, including acute myocardial infarction, ischemic and non-ischemic cardiomyopathy, valvular heart disease (including prosthetic valves and infective endocarditis), patent foramen ovale and atrial septal aneurysm (ASA), cardiac tumors, and aortic atherosclerosis.

A meta-analysis indicates that the risk of ischemic stroke after acute myocardial infarction is 11.1/1000 (95% *CI:* 10.7-11.5) during hospitalization, 12.2/1000 (95% *CI:* 10.4-14.0) within 30 days of onset, and 21.4/1000 (95% *CI:* 14.1-28.7) within 1 year of onset [357].The factors related to embolism are anterior wall infarction and left ventricular thrombosis. Studies found that the incidence of left ventricular thrombosis

was 6%-15% in patients with anterior wall infarction, and about 27% in patients with anterior wall infarction complicated with left ventricular ejection fraction < 40% [358-360]. Systemic embolism will occur in about 11% of patients with left ventricular thrombosis [361].

Stroke occurs at an annual rate of 1% in cardiomyopathy patients with sinus rhythm [362-364]. Causes of cardiomyopathy include infection, heredity and valvular heart disease, coronary artery disease, hypertension and tachycardia, which eventually lead to myocardial dysfunction and even congestive heart failure [365].Left ventricular dysfunction leads to mural thrombus and then causes embolism events.

The annual incidence of systemic embolism events in patients with rheumatic valvular disease is 1.5%-4.7% [366]. Thrombosis and subsequent embolism events are more likely due to enlarged left atrium. The reported conclusions on the association between mitral valve prolapse and cerebral embolism are inconsistent [367-369]. A population-based study in the United States found a higher risk of stroke and TIA among patients with mitral valve prolapse in sinus rhythm (*RR*=2.2, 95% *CI:* 1.5~3.2) [370], and independent risk factors were older age, mitral thickening and atrial fibrillation. According to a data analysis from the Framingham Study, mitral annulus calcification was associated with a relative risk of stroke (RR=2.1, 95% *CI:* 1.2~3.6) [371]， and independent risk factor was the severity of mitral annular calcification. An Amerindian cohort study also suggested that mitral annulus calcification increased stroke risk (*RR*=3.1, 95% *CI:* 1.8~5.2) [372]. In contrast, a multi-ethnic study found

that mitral annulus calcification was associated with myocardial infarction and vascular death rather than ischemic stroke [373]. At present, there is no evidence that anticoagulant therapy can reduce stroke risk in patients with mitral annulus calcification. Embolism events caused by calcification of aortic stenosis are uncommon unless interfered by valvuloplasty, transcatheter or surgical valve replacement [374].

The heart valve prosthesis can be a source of embolus. Mechanical valves have higher risk to embolize than biological valves. The incidence of embolic events among biological valve patients in sinus rhythm is about 0.7% every year [375]. Biovalve-related embolic events usually occur within 3 months after operation and are more common in mitral valve than in aortic valve [376].

Embolism occurs in 20%-40% of patients with endocarditis, most of which causes central nervous system damage [377-378]. Embolism events are greatly reduced after anti-infection treatment [379-381]. The related risk factors were excrescence size, mitral valve involvement and staphylococcus aureus infection[379-380, 382].

Primary benign tumours of the heart (such as myxoma and papillary fibroma) and primary malignant tumours (such as sarcoma) can form emboli and cause ischemic stroke [383-384]. Tumours with fragile surfaces in the cardiac chamber are more prone to embolism. Myxoma is the most common cardiac tumour, and is often found in the left atrium [385]. 30%-40% of myxoma will be complicated with embolism [386]. Stroke and TIA are the first symptoms in half of cardiac papillary fibroma patients [387-388].

Aortic atherosclerotic plaques ≥ 4mm, especially large and complex plaques, are associated with the increased risk of cryptogenic stroke [388-392]. A French study found that aortic atherosclerosis plaques > 4 mm can independently predict stroke recurrence (*RR*=3.8, 95%*CI:* 1.8~7.8) [393]. In the PICSS study, it was found that large plaques detected by transoesophageal echocardiography were associated with a significantly increased risk of recurrent stroke or death during a 2-year follow-up (RR=6.42, 95%*CI:* 1.62-25.46), which also existed in patients with large complex plaques (*RR*=9.50, 95%*CI:* 1.92~47.10) [390]. Atherosclerotic embolism caused by atherosclerotic plaques is the cause of stroke associated with cardiac surgery [390-392, 394].

Various types of cardiac surgery are also important risk factors for embolism. Cardiac surgery such as valve replacement, coronary artery bypass grafting, radiofrequency ablation and labyrinthine surgery had a high incidence of perioperative embolism. Embolic sources can be either the operation itself or the implants. And embolism is mostly related to secondary atrial fibrillation [395-401]. Anticoagulant therapy during perioperative period can improve prognosis[441].

Among the common cardiac structure assessment methods, ordinary chest X-ray examination can observe the atrioventricular enlargement and pulmonary oedema through mediastinum. Transthoracic ultrasonography can better detect left ventricular thrombosis than transoesophageal ultrasonography, while transoesophageal ultrasonography can better reflect left atrial appendage thrombosis and patent foramen

ovale[403]. Transoesophageal ultrasonography can also identify left atrial appendage morphology, which is associated with embolus formation [404]. Cardiac magnetic resonance can further show potential embolic sources that cannot be shown by cardiac cardiac ultrasonography. In a prospective study, about 21% of patients originally considered as cryptogenic stroke were redefined as cardiogenic embolism after routine examination. [405]. Cardiac magnetic resonance is very sensitive to left ventricular thrombosis, and can also detect embolic sources such as ventricular noncompaction insufficiency, atrial fibrosis, and complex atherosclerotic plaque [406-409].

Recommendation:

[1] All stroke patients should complete routine chest X-ray and transthoracic echocardiography in order to detect possible cardiac structural diseases (Class I, Level of Evidence C).

[2] For stroke patients with suspected cardiogenic embolism, performing transesophageal ultrasonography to determine the presence of left auricular thrombosis, PFO or interatrial septal aneurysm is reasonable (Class IIa, Level of Evidence B).

[3] Transthoracic echocardiography cannot be replaced by transesophageal echocardiography (Class III, Level of Evidence C).

[4] Cardiac MRI is effective in identifying the etiology of cryptogenic stroke. It can be carried out in hospitals which can do cardiac MRI (Class IIb, Level of Evidence B).

[5] Specific heart lesions found during cardiac screening in stroke patients should be actively guided in specialized individual treatment (Class I, Level of Evidence B).

2. Cardiac rhythm assessment

It is reported that the incidence of atrial fibrillation in Asian population is lower than that of white people (~1% vs. ~2%), but the overall disease burden is still high due to the aging population [410-411]. Even if there are no other cardiac diseases, atrial fibrillation induces thrombus in left atrial appendage and increases the stroke risk by 4-5 times[412]. Embolism caused by atrial fibrillation accounts for more than half of all cerebral embolism events. Asymptomatic atrial fibrillation and arrhythmia are very common [413-415].A cohort study shows that about half (47%) of atrial fibrillation patients were diagnosed after ischemic stroke [416].Patients with cardiogenic cerebral embolism caused by atrial fibrillation have larger infarction area and higher haemorrhagic transformation rate and mortality rate, causing greater nursing burden [417-425].

Different from atrial fibrillation, the relationship of paroxysmal supraventricular tachycardia, atrial flutter, sick sinus syndrome with stroke is unknown. Some studies

have reported that the annual incidence of stroke in patients with paroxysmal atrial fibrillation, supraventricular tachycardia was similar to patients with persistent atrial fibrillation, ranging from 1.5% to 3.3% [426-431]. Another retrospective cohort study found that paroxysmal supraventricular tachycardia was associated with ischemic stroke [432]. Other arrhythmias associated with increased risk of stroke have also been reported, such as Bayes syndrome, and intra-atrial block. To date, there is no evidence to prove that intervention on arrhythmia can reduce the occurrence of stroke[433-436]. Stroke risk assessment tools for patients with atrial fibrillation can effectively predict the occurrence of clinical adverse events based on specific risk factors and can guide treatment decisions. [437]. CHADS2 has been proved to be a simple and effective tool for stroke risk assessment in patients with atrial fibrillation. Fully validated independent risk factors for stroke in atrial fibrillation are used for assessment [81,438]. The full score is 6. Specifically, congestive heart failure, hypertension, age > 75, diabetes each score 1 point, prior stroke or TIA scores 2 points. This score has been confirmed in many cohort studies of atrial fibrillation. The stroke risk of patients with atrial fibrillation is divided into the high-risk group (≥ 2 points, 1.9%-7.6%/year), moderate-risk group (1 point, 1.2%-2.2%/year) and low-risk group (0 point, 0.5%-1.7%/year) according to CHADS2 [438-441]. CHA2DS2-VASc sets vascular diseases (peripheral vascular disease, myocardial infarction, aortic plaque), aged 65-75 years and women each scores 1 point, which is more sensitive to embolic events than CHADS2 score [442-443].The CHA2DS2-VASc score is a good assessment tool for

stroke and TIA risk in patients with atrial fibrillation, and is applicable even in patients with end-stage renal disease and heart failure without atrial fibrillation [444-445]. The absolute risk of stroke was included in the risk assessment, which is of guiding significance for the formulation of complex drug interventions.

Studies showed that the detection rate of undiagnosed atrial fibrillation can be increased in patients aged ＞65 years who are admitted to primary health care institutions through professional pulse assessment. [446-447]. Routine systematic pulse examination in the outpatient department and 12-lead ECG examination for patients with irregular pulse rhythm can increase the diagnostic rate of atrial fibrillation by 60% [446]. The application of long-term ECG monitoring in cryptogenic stroke is mainly used to detect paroxysmal atrial fibrillation. Continuous ECG monitoring, repeated ECG examination and 24h Holter monitoring are the first-line diagnostic procedures within 48 to 72h after the onset of stroke. If embolism is suspected and no other reasons are found, there are various methods to prolong ECG monitoring, such as implanting a loop recorder in vitro or in vivo, or reading pacemaker or defibrillator data through external telemetry, etc. [448-449]. Studies showed that extending the monitoring time of heart rhythm to 10 days, 30 days or even 6 months will greatly increase the detection rate of paroxysmal atrial fibrillation. But at the same time, the risk of over-diagnosis will increase, because only paroxysmal atrial fibrillation exceeding 30 seconds is meaningful to embolism events [450-452]. The TRENDS study reported that in the long-term monitoring, patients with burden of atrial fibrillation or

atrial tachycardia > 5.5h within 30 days had a doubled risk of cerebral and systemic embolism events [453]. The trial of portable examination equipment for people at a high risk of atrial fibrillation is underway and the results are expected [454]. Atrial fibrillation may runs in family, and genetic screening for patients with high risk for atrial fibrillation may be possible in the future [455].

Recommendations

[1] Asymptomatic atrial fibrillation and arrhythmia are very common, screening for atrial fibrillation should be routinely performed in the clinic, the routine checking of pulse should be performed on a patient > 65 years old, and a 12-lead ECG should be conducted on patients with abnormalities of pulses (Class I, Level of Evidence A).

[2] The CHADS2 or CHA2DS2 - VASc score is recommended for patients with persistent atrial fibrillation when assessing for the risk of stroke, and used to guide intervention (Class I, Level of Evidence A).

[3] In patients with latent stroke who may have embolism, 24h or long term and remote cardiac monitoring aiming to find any paroxysmal atrial fibrillation is reasonable (Class IIa, Level of Evidence B).

[4] For patients with non-persistent atrial fibrillation or paroxysmal atrial fibrillation/atrial tachycardia (> 5.5h) within 30 days or paroxysmal atrial fibrillation for more than 30 seconds, stroke prevention treatment as in patient

with persistent atrial fibrillation may be reasonable (Class IIb, Level of Evidence B)

[5] Whether arrhythmias other than atrial fibrillation or paroxysmal supraventricular tachycardia are associated with embolic events is unclear, and any intervention of those arrhythmias to reduce the incidence of embolism is still inadequate, symptomatic treatment can be taken into consideration (Class III, Level of Evidence C).

3. Cardiac function assessment

Cardiac dysfunction is usually secondary to organic heart disease or various arrhythmias that affect myocardial coordination. Even in sinus rhythm patients without left atrial enlargement [456-458], decreased blood flow velocity in left atrium and left atrial appendage also increases the risk of embolic stroke. In patients with atrial fibrillation, the stroke risk increases as the left atrium enlarges and the left atrial emptying fraction decreases. Even in patients with normal left atrium size and sinus rhythm, left atrial dysfunction also exists and the risk of stroke is increased [459]. Left atrial spontaneous echo contrast (LASEC) is associated with thrombosis, and rheumatic heart disease patients with LASEC have a higher CHA2DS2 - VASc average than patients without LASEC [460]. Patients in sinus rhythm have moderate or severe decrease of left ventricular systolic function (EF ≤ 35%) and a flow rate of left atrial appendage ≤ 55cm/s, which is easy to induce LASEC, and they are high risk

populations for stroke [461].Von Willebrand factor (vWF) plays a role in left atrial flow velocity reduction and thrombosis, and is relatively high in plasma of patients with atrial fibrillation [462-463].For ischemic stroke patients complicated with paroxysmal atrial tachycardia, the enlarged left atrial volume index is an independent risk factor for atrial fibrillation, which can predict the recurrence of stroke. It is suggested that 24h Holter monitoring and appropriate anticoagulant therapy be performed for the above patients [464].

Recommendations

[1] It is recommended to include cardiac function in the cardiac assessment of stroke patients: the left atrium, left atrium, left ventricle function, specific projects including volume index, emptying index and blood flow velocity (Class I, Level of Evidence B).

[2] The left atrium, left auricle and left ventricular blood flow disturbance, and left atrial spontaneous ultrasound contrast phenomenon are independent risk factors for embolus formation and triggering embolism. It is necessary to find the cause and take intervention measures actively (Class IIa, Level of Evidence B).

(III) Examination and assessment of cryptogenic stroke

About 80% of patients with cryptogenic stroke are neither related to lacunar (caused

by arteriolar diseases) nor severe atherosclerotic stenosis, and have no major source of cardiac embolism (such as atrial fibrillation). A recent monitoring and imaging study showed that most of these patients had potential embolic sources, suggesting that a large proportion of cryptogenic stroke in the past can be described as embolic stroke of undetermined source (ESUS) [465]. ESUS patients are embolic stroke and their major risks of cardiogenic embolism, occlusive atherosclerotic stroke and lacunar stroke are excluded by sufficient diagnostic assessment. Potential causes of ESUS include low-risk potential cardiac embolism [myxomatous valve prolapse, mitral valve calcification, aortic stenosis, calcified aortic valve, cardiac arrest, sick sinus syndrome, atrial fast rhythm, left atrial appendage stagnation with reduced blood flow velocity, spontaneous hypoecho, atrial septal aneurysm, Chiari network, moderate systolic or diastolic dysfunction of left ventricle (diffuse/focal), ventricular non-contraction and endocardial myocardial fibrosis], latent paroxysmal atrial fibrillation, arterial embolism (atherosclerotic plaque in the aortic arch and cerebral artery non-stenotic ulcer plaque), abnormal embolism (patent foramen ovale, atrial septal defect and pulmonary arteriovenous fistula), tumor-related and unknown causes. See Figure 8 for the diagnostic flow of ESUS.

II. Risk factor assessment and risk stratification

(I) Blood pressure assessment

About 80% of patients have elevated blood pressure after AIS. The blood pressure level of patients and the timing of initiating antihypertensive therapy for patients are

closely related to prognosis. Therefore, blood pressure assessment after onset is of great significance.

In terms of baseline blood pressure after ischemic stroke, some studies have shown that higher baseline blood pressure is related to good prognosis, while low blood pressure variability in the early phase (within 72 hours) is independently related to good prognosis [466-472]. In addition, the study showed that the relationship between blood pressure and prognosis was due to U-shaped effect. With a limit of 180/100mmHg, patients with the highest or lowest values of SBP and DBP had a higher frequency of adverse prognosis [473]. For patients with culprit artery stenosis less than 50%, elevated pulse pressure at the early stage is independently associated with unfavorable late outcome[474]. And follow-up of a large sample study showed a J-shaped effect between pulse pressure and recurrence of cardiovascular events [475]. For patients with severe arterial stenosis, antihypertensive therapy is associated with stroke progression and poor prognosis [476].

Recommendations

[1] Hypertension after AIS should be moderated strictly and lowered moderately, controlling the blood pressure in 140~160/80~99 mmHg within 24~48h is reasonable (Class I, Level of Evidence A).

[2] Blood pressure variation and pulse pressure should be monitored closely after AIS. Blood pressure correlates the prognosis (Class IIa, Level of Evidence B).

(II) Assessment of blood lipid

Assessment of blood lipid after AIS is helpful to judge the pathogenesis and guide the treatment in the secondary prevention of ischemic stroke. At present, various reports suggest that blood lipid should be controlled at the low level of normal range, especially the relatively high level of low-density lipoprotein which requires intensive lipid-lowering therapy (the target value for lowering is set as LDL-C concentration < 1.8mmol/L or > 50% lower than baseline). A large sample size randomized controlled study showed that intensive lipid-lowering therapy can reduce the recurrence of stroke after ischemic stroke, but may increase the risk of haemorrhage [477]， and many small sample studies also confirmed this result. [478-481]. Another large sample size cohort study also found that high-dose atorvastatin increased the risk of haemorrhage, but was not correlated with baseline or recent LDL-C [482]. However some small sample studies found that [483-485] the lower baseline blood lipid at admission indicates that cerebral infarction was more serious [486-487], and dyslipidaemia (high or low) was associated with poor prognosis [488-491]. Meanwhile, a large sample size multi-center cross-sectional study showed that the up-to-standard rate of blood lipid after stroke (< 1.8mmol/L) was still relatively low, which was about 27.4% in China, and drug therapy and health education still need to be vigorously promoted [492-495].

Recommendations

[1] Dyslipidemia (too high or too low) is closely related to poor prognosis. Serum lipid level should be actively assessed after AIS, in order to guide lipid-lowering treatment and secondary prevention (Class IIa, Level of Evidence B).

[2] Relatively low blood lipids may indicate that the condition of cerebral infarction is more serious, and attention should be paid to the changes of patients' condition (Class IIb, Level of Evidence C).

[3] At present, the rate of reaching the standard of blood lipid control after AIS in China is still low, blood lipid control should be strengthened, at the same time pay attention to regular monitoring to avoid bleeding transformation (Class I, Level of Evidence B)

(III) Assessment of abnormal glucose metabolism

Many studies and meta-analysis have shown that hyperglycaemia (≥ 7.7mmol/L) after stroke, history of diabetes and high blood glucose fluctuation were closely related to low recanalization rate after thrombolysis and worse clinical outcome [534-554]. The blood glucose level may indicate the severity of the disease [496-497]. However, β-cell dysfunction was associated with an increased risk of poor prognosis in nondiabetic patients with ischemic stroke[498]. Some small-sample RCT showed that it was feasible and tolerable to inject insulin within 48 hours to control blood glucose strictly (5-8 mmol/L), which can improve stroke prognosis [499-500]. A small-sample RCT found that intravenous infusion of glucose-insulin-potassium solution can reduce

blood glucose and improve the brain lactic acid level, but cannot improve stroke progression [501]. Some studies have also shown that insulin pumping for hypoglycaemic therapy after stroke and health education for diabetic patients can benefits from controlling blood glucose. The incidence of hypoglycaemia after stroke is relatively low. But if it occurs, it will directly aggravate cerebral ischemia injury and cerebral ooedema, leading to poor prognosis. Therefore, blood glucose should be closely monitored to prevent hypoglycaemia.

Recommendations

[1] High blood sugar level and blood sugar fluctuation after AIS is closely related to the prognosis. Clinical monitoring and strict glycemic control are recommended (Class I, Level of Evidence A).

[2] Blood glucose should be strictly monitored after AIS and insulin should be recommended for stable hyperglycemic control, it is reasonable to control the blood glucose concentration to 5 ~ 8 mmol/L (Class IIa, Level of Evidence B).

(IV) Risk stratification assessment of TIA

1. California risk score In 2000, a cohort study of 1707 TIA patients showed that 180 patients had recurrent stroke within 90 days. From the data, independent risk factors were screened through multivariable logistic regression analysis, and California risk score was established: A. Age > 60 years; B. Diabetes; C. Duration of

symptoms › 10min; D. Symptom of physical weakness; E. Speech impairment. It is used to predict the short-term stroke risk of TIA patients and the highest score is 5.

2. SPI-I and SPI-II risk scores In 1991, Kernan et al established the SPI-I score and scored and followed up 142 TIA and minor stroke patients to predict the risk of stroke and death within 2 years after symptoms onset. The score included: A. Age › 65 (3 points); B. Diabetes (3 points); C. Blood pressure › 180/100 mmHg (2 points), D. Coronary atherosclerotic heart disease (1 point); E. The first event was stroke or TIA (2 points). The highest score was 11. In low risk group (0-2 points), intermediate risk group (3-6 points) and high-risk group (7-11 points), corresponding outcome rates were 3%, 27%, and 48% in the original cohort and 10%, 21%, 59% in the test cohort respectively.

Then, on the basis of the SPI-I score, past stroke history (3 points) and congestive heart failure (3 points) were added to establish the SPI-II score [502], with a maximum of 15 points, to evaluate the incidence of stroke or death within 2 years.

3. Essen stroke risk score Essen Stroke Risk Score (ESRS) is developed based on the CAPRIE test database and is one of the few prediction tools for judging stroke recurrence risk based on the ischemic stroke population. Its content includes: A. 65-75 years old; B. › 75 years old; C. Hypertension; D. Diabetes; E. Previous myocardial infarction; F. Other cardiovascular diseases; G. Peripheral arterial diseases; H. Smoking; I. Previous TIA or ischemic stroke; Specifically, except for B. › 75 years old whose score is 2 points, the others score 1 point, and the highest score is 9.

Patients are divided into the low risk group (0-2) and high-risk group (≥ 3). At present, the score is also applied to predict the recurrence risk in patients with TIA and minor stroke [503].

4. ABCD score system California, SPI-I, SPI-II and Essen scores all predict long-term prognosis. However, recurrent stroke often occurs in a short period of time for TIA patients. Therefore Rothwell et al. established the ABCD score to predict stroke risk within 7 days after TIA, and on this basis, ABCD2, ABCD2-MRI, ABCD2-I, ABCD3 and other scores were established.

(1) ABCD score [567]: Based on the Oxford Shire Community Stroke Project (OCSP), ABCD score was established to predict the risk of stroke within 7 days after TIA, with a total score of 6, including:

A. Age ≥ 60 (1 point).

B. Blood pressure: SBP > 140mmHg and/or DBP ≥ 90mmHg (1 point).

C. Clinical manifestations: unilateral limb weakness (2 points), speech disorder without limb weakness (1 point), other symptoms (0 point).

D. Symptoms lasting for > 60 min (2 min), 10-59 min (1 point), and < 10 min (0 point).

The predictive value of the ABCD score was validated in OXVASC study. The results showed that the 7-day risk of stroke was 0.4% in patients with an ABCD2 score of more than 5, 12.1% with a score of 5, and 31.4% with a score of 6. It suggested that the higher the ABCD score of TIA patients, the higher the risk of stroke within 7 days.

Rothwell et al. suggested that patients with ABCD score ≤ 4 generally do not need hospitalization observation, while patients with a score of 6 are in the acute phase of disease and need to be hospitalized for observation and treatment [504].

(2) ABCD2 score: Based on the California risk score and ABCD score, ABCD2 score was proposed to predict the risk of stroke within 2 days after TIA. Compared with the ABCD score, the ABCD2 score increases the risk factor of diabetes (1 point), with a total score of 7 points. At the same time, the stroke risks of 2,893 TIA patients in 4 groups of cohorts were predicted for 2 days, 7 days, 30 days and 90 days. The results showed that the stroke risks of the high-risk group (6-7 points), intermediate risk group (4-5 points) and low risk group (0-3 points) within 2 days after TIA were 8.1%, 4.1% and 1.0% respectively, indicating that the ABCD2 score can be used to predict the early stroke of TIA patients. However, ABCD2 has limited effect on the assessment of early recurrent stroke in patients with mild stroke. This result is based on the Oxford Vascular study that evaluated the predictive value of ABCD2 and other scoring systems for 7d and 90d recurrence risk of patients with mild stroke (NIHSS ≤ 5). The study results showed that the predictive value of ABCD2 was of a medium level [505].

(3) ABCD2-MRI and ABCD2-I score: With the rapid development of imaging technology, CT and MRI have become an important method for clinical diagnosis and prognosis evaluation of cerebrovascular diseases. Combining imaging markers with the ABCD scoring system can improve the prediction level.

In 2008, researchers established the ABCD2-MRI score based on the ABCD2 score and imaging markers. The score added the intracranial artery stenosis and DWI high signal, each with a score of 1. 180 TIA or mild stroke patients were examined by head MRI (images within 24 hours after onset) and scored. The results showed that 11.1% of the patients had recurrent stroke events within 90 days after onset. Specifically, the recurrent stroke rates for 90 days in the high-risk group (7-9 points), intermediate risk group (5-6 points) and low risk group (0-4 points) were 32.1%, 5.4% and 0.0% respectively. Meanwhile, the rate of dysfunction within 90 days was 22.9%, 7.5% and 7.7% respectively. However, the ABCD2 score could not predict dysfunction of the NICE patients. Therefore, based on clinical and MRI information within an effective time window, it is possible to more accurately predict the risk of recurrent stroke after TIA or minor stroke. In 2010, the ABCD2-I score added DWI high signal based on the ABCD2 score and assigned 3 points to it, and 4,574 TIA patients were predicted for stroke risk. The results showed that the ABCD2-I score improved the predictive value for stroke risk within 7 days and 90 days after TIA compared with ABCD2 [506]. (4) ABCD3 and ABCD3-I score: The ABCD3 score was proposed according to the ABCD2 score[507].The ABCD3 score adds two factors to the ABCD2 score: treatment of TIA patients within 7 days before onset and occurrence of TIA at least once before, with a total score of 0-9 points. Researchers found that the ABCD3 score and ABCD2 score have similar predictive value for stroke recurrence risk within 7 days and 90 days after TIA. However, the ABCD3 score can not to be wide use yet because the

validity test has not been conducted.

Meanwhile, on the basis of the ABCD3 score, ipsilateral carotid stenosis and DWI abnormal high signal were added in ABCD3-I score. It was established to predict the stroke risk of 886 TIA patients. The results showed that the ABCD3-I score improved the prediction accuracy compared with the ABCD2 score.

(5) ABCDE+ score: Recently, some researchers added etiological classification and imaging findings to the ABCD2 score and established the ABCDE+ score. This is the first score that added etiological classification into the ABCD scoring system. In 248 TIA models, the AUC value of the ABCDE+ score was higher than that of the ABCD2 score (P=0.04). However, this score has not been widely accepted yet.

Among the many risk models, the ABCD scoring system is the most widely used. Specifically, the ABCD2 score can well predict the short-term stroke risk of TIA patients, and is the most widely used. Its predictive value has been verified, and it has been recommended by the expert consensus in China. The ABCD2-I, ABCD2-DWI and ABCDE+ scores have rarely been verified in Chinese population. The ABCD3 and ABCD3-I scores are rarely used, which can more effectively assess the short-term stroke risk of TIA patients.

(V) Stratified assessment of ischemic stroke

1. Atherosclerotic cardiovascular disease (ASCVD) The definition of clinically confirmed ASCVD includes:

(1) Acute coronary syndrome

(2) History of myocardial infarction

(3) Stable or unstable angina pectoris

(4) Coronary artery or other vascular reconstruction

(5) Atherosclerotic stroke or TIA

(6) Atherosclerotic peripheral arterial disease

2. Essen stroke risk score [503](Supplemental Table 10) It is used to assess the risk of stroke recurrence in patients with non-cardiogenic ischemic stroke, thus giving individualized secondary prevention measures to different patients. The total score is 9 points, 0-2 for low risk, 3-6 for intermediate risk and 7-9 for high risk.

3. Risk stratification assessment of atrial fibrillation

(1) CHADS2 score and CHA2DS2-VASc score [508-510](Supplemental Table 11) **:** It is mainly used to assess the risk of stroke in patients with atrial fibrillation and guide antithrombotic therapy.

Classic CHADS2 score: Patients with the total score of more than 2 are high risk group for stroke, and anticoagulant therapy is recommended. Patients with the total score of 1~2 points are intermediate risk group, and anticoagulant therapy or antiplatelet therapy can be selected, and anticoagulant therapy is recommended. Patients with the total score of 0 are low risk group and antiplatelet therapy is recommended.

Modified CHADS2 score: Lip et al. modified the stratification standard as 0 for low risk, 1 for intermediate risk and 2-6 for high risk.

The CHA2DS2-VASc score adds the risk factor of gender and refines the age stratification: 0 point for the low risk group, 1 for the intermediate risk group and 2--6 for the high-risk group.

See Supplemental Table 12 for a summary of stratification assessment of stroke risks for patients with atrial fibrillation.

(2) HAS-BLED scale [511]: It is mainly used to assess the bleeding risk of anticoagulant therapy for patients with atrial fibrillation. The scale has a total score of 9 points, with a score ≥ 3 for high risk, 1-2 for intermediate risk, and 0 for low risk (Supplemental Table 13).

When the CHADS2 score is ≥ 2, the patients have a high risk of stroke, and anticoagulant therapy is recommended. If the HAS-BLED score is higher than CHADS2 score, the bleeding risk exceeds the anticoagulant benefit. For patients with CHADS2 score =1, the difference between the HAS-BLED score and CHADS2 score is no more than 2 points, and the anticoagulant benefit is greater than the bleeding risk.

4. SPI-II scale SPI-II is used to predict the risk of long-term stroke recurrence. However, the scale is of little value in predicting the risk of stroke recurrence within 90 days after the minor stroke (NIHSS score < 3). The total score is 15 points, 0-3 for low risk, 4-7 for intermediate risk, and 8-15 for high risk **(Supplemental Table 14)**.

III. Diagnosis of aaetiology and pathogenesis

The aaetiology of ischemic stroke is complex and diverse, and it is usually difficult for a single classification standard to include all subtypes of stroke. Reasonable and feasible ischemic stroke classification is very important to evaluate therapeutic effects in clinical trials. In the past, the classification systems developed by western countries were all based on white race, and their main mechanisms of stroke were cardiogenic embolism or extracranial atherosclerosis. However, these classification systems may not be applicable to Asian populations. The typing proportion of ischemic stroke is related to race. Stroke data from western countries show that cardiogenic embolism is the most important cause of ischemic stroke. In addition, the incidence of extracranial atherosclerotic stenosis in American population is significantly higher than that of intracranial atherosclerosis.

After the classical TOAST classification [80,512] system, various derivatives have been generated successively, such as SSS-TOAST classification[88], CCS-TOAST classification[72], South Korea -TOAST classification, etc. But the Chinese ischemic stroke subtype CISS classification, which is defined and developed independently by China [513] is currently the most suitable classification method for the aaetiology and pathogenesis of Chinese population. The classification process of the standard system is divided into two steps: The first step is similar to the classical TOAST classification, and causes are also divided into five types including large artery

atherosclerosis (LAA), cardiogenic stroke (CS), penetrating artery disease (PAD), other causes (OE) and undetermined aaetiology (UE). Specifically, LAA is also divided into aortic arch atherosclerosis and intra- and extracranial large arteries atherosclerosis by site. In the second step, the pathogenesis of intracranial and extracranial atherosclerotic cerebral infarction is classified into 4 types including parent artery (plaque or thrombus) occluding penetrating artery, artery to artery embolism, hemodynamic/impaired emboli clearance and multiple mechanism.

(I) Large artery atherosclerosis

In CISS classification, large artery atherosclerosis includes aortic arch atherosclerosis and intra- and extracranial large arteries atherosclerosis.

1. Aortic arch atherosclerosis

(1) Acute multiple infarction lesions, especially involving bilateral anterior and/or anterior and posterior circulations.

(2) No evidence of atherosclerosis of relevant intracranial or extracranial large arteries (vulnerable plaques or stenosis ⩾50% or occlusion).

(3) No evidence of potential cause of cardiogenic stroke (CS).

(4) No evidence of other aetiologies that can cause multifocal acute ischemic infarcts such as vasculitidies, haemostatic disturbances, and tumorous embolism.

(5) Evidence of significant aortic arch atherosclerosis: aortic plaques 24 mm and/or aortic thrombi, detected by high resolution magnetic resonance (HR-MRI)/ MRA and/or transoesophageal ultrasound (TEE).

2. Intra- and extracranial large arteries atherosclerosis

(1) Any distribution of acute infarcts (except isolated infarct in the territory of one penetrating artery), with evidence of atherosclerosis involving intracranial or extracranial large arteries (vulnerable plaques or stenosis ≥50%) that supply the area of infarction.

(2) Concerning isolated penetrating artery territory infarct, the following circumstance should also be included in LAA: with evidence of atherosclerotic plaque (detected by HR-MRI) or any degree of stenosis in the parent artery (detected by TCD, MRA, CTA, or DSA).

(3) No evidence of potential cardiac-origin embolic cause.

(4) Other possible causes have also been excluded.

(II) Cardiogenic stroke

1. Diagnostic criteria

(1) Acute multiple infarcts, especially involving bilateral anterior and/or anterior and posterior circulations (including cortical infarcts) that have occurred closely in time.

(2) No evidence of atherosclerosis on relevant intracranial or extracranial large arteries (vulnerable plaques or stenosis ≥50% or occlusion).

(3) No evidence of other aetiologies that can cause multifocal acute ischemic infarcts such as vasculitidies, haemostatic disturbances, and tumorous embolism.

(4) Evidence of cardiac disease that has a potential for embolism.

(5) If the possibility of aortic arch atherosclerosis has been excluded, CS is definite.

Otherwise, the category should be possible CS.

2. The potential lesions included under this category are: mitral stenosis, prosthetic heart valve, myocardial infarction within the past 4 weeks, mural thrombus in the left cavities, left ventricular aneurysm, any documented history of permanent or transient atrial fibrillation or flutter with or without spontaneous echo contrast or left atrial thrombus, sick sinus syndrome, dilated cardiomyopathy, ejection fraction <35%, endocarditis, intracardiac mass, PFO plus in situ thrombosis, PFO plus concomitant PE, or DVT preceding the brain infarction.

(III) Perforating artery disease

Acute isolated infarct in the territory of one penetrating artery caused by atherosclerosis at the proximal segment of the penetrating arteries or lipohyalinotic degeneration of arterioles is called penetrating artery disease (PAD). Diagnostic criteria: (1) Acute isolated infarct in clinically relevant territory of one penetrating artery, regardless of the size of infarct. (2) No evidence of atherosclerotic plaque (detected by HR-MRI) or any degree of stenosis in the parent artery (detected by TCD, MRA, CTA, or DSA). (3) With evidence of vulnerable plaques or stenosis ≥50% in ipsilateral proximal intracranial or extracranial large arteries, isolated penetrating artery infarct is classified in undetermined aaetiology (UE; multiple aaetiology). (4) With evidence of cardiac disease that has a potential for embolism, isolated penetrating infarct is classified in UE (multiple aaetiology). ⑤ Other possible causes has been excluded.

(IV) Other aetiologies

Evidence of other specific diseases (e.g., vascular related disease, infective disorder, inherited disease, haematological system disorder, vasculitis), that are relevant to the index stroke and can be demonstrated by blood tests, cerebrospinal fluid (CSF) tests, and vascular imaging. The possibility of LAA or CS has been excluded.

(V) Undetermined aaetiology

1. No evidence of any specific potential aaetiology that is clinically relevant to the index stroke.

2. Multiple: Evidence of more than one potential cause, but difficult to determine which was the relevant cause of the index stroke.

3. Unknown: No determined cause is responsible for the index stroke unless more investigations would be performed.

Section 8 Intervention on aaetiology and pathogenesis

I. Aortic atherosclerotic stroke

(I) Antithrombotic therapy

Antiplatelet drugs combined with risk factor control are the main drug treatment plans for patients with aortic atherosclerotic stroke. Aspirin is currently the most commonly used antiplatelet drug worldwide.

In recent years, the use of dual antiplatelet drugs in patients with aortic atherosclerotic stroke is increasing, especially in patients with intracranial arterial stenosis. The evidence mainly comes from the following research results: Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) [514], Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) [515] and Warfarin-Aspirin for Symptomatic Intracranial Disease (WASID) [516].

In 2011, the large-scale randomized study SAMMPRIS compared the effect of intracranial arterial stenting and intensive drug therapy for symptomatic severe intracranial arterial stenosis on reducing stroke recurrence and mortality. The patients were divided into two groups. One group was treated with intensive drug therapy, and the other group was treated through stenting in addition to intensive drug therapy. Drug therapy included aspirin (325 mg/d) and clopidogrel (75 mg/d) for 90 days. Meanwhile, major risk factors such as hypertension and hypercholesterolemia as well as secondary risk factors such as diabetes, smoking, overweight and insufficient

exercise were managed through lifestyle adjustment. The results showed that the 30-day stroke recurrence or death rate in the interventional treatment group was significantly higher than that in the medical treatment group, and the incidence rate of major endpoint events in the interventional treatment group was also significantly higher after 1-5 years of follow-up. After correcting baseline characteristics, Chaturvedi et al. found that stroke or vascular death within 30 days in patients with intracranial arterial stenosis who took aspirin or warfarin orally in the WASID study was 1.9 times that in patients who took dual antiplatelet therapy orally in the SAMMPRIS study, thus providing theoretical support for intensified drug therapy. Another evidence for dual antiplatelet therapy comes from "Clopidogrel Plus Aspirin versus Aspirin Alone for Reducing Embolization in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis" (CLAIR). The results of this study suggested that in the intracranial atherosclerosis subgroup, the number of microembolic signals detected by transcranial Doppler (TCD) was reduced (31% vs. 54%) in patients treated with clopidogrel combined with aspirin compared with patients treated with aspirin alone. The subgroup analysis of "Clopidogrel in High-risk Patients With Acute Non-disabling Cerebrovascular Events" (CHANCE) found that patients with intracranial artery stenosis using dual antiplatelet drugs to prevent stroke recurrence had a tendency for good prognosis at 90 days compared with patients using aspirin alone [517]. For patients with stroke or TIA caused by severe intracranial arterial stenosis (70%-99%), use of aspirin combined with clopidogrel (75mg/d) for 90 days

may be reasonable.

Patients with stable coronary heart disease are high-risk groups for stroke, myocardial infarction and vascular death. For a long time, although aspirin has been used as the standard antithrombotic therapy, there have still been a considerable number of cardiovascular events. Recently, breakthroughs have been made in the research and development of oral factor Xa inhibitors. Previous studies have shown that aspirin or other antiplatelet drugs combined with low-dose rivaroxaban can be beneficial for patients with acute coronary syndrome. Deeper understanding of whether low-dose rivaroxaban combined with aspirin will further reduce the residual risk of cardiovascular events in patients with coronary heart disease is needed.

The COMPASS study [518] is the first randomized, double-blind, multicentre, prospective and randomized Phase III clinical study to evaluate the efficacy and safety of new oral anticoagulants in the high-risk patient population of coronary artery disease (CAD) or peripheral artery disease (PAD). A total of 27,400 CAD or PAD patients were enrolled in the study and randomly divided into 3 groups. The present treatment group included 2 groups: Rivaroxaban 2.5mg orally bid, plus aspirin 100mg bid; Rivaroxaban 5mg orally bid; Aspirin 100mg orally qd. The primary efficacy endpoint of the study was first occurrence of cardiovascular death, myocardial infarction and stroke, the primary safety endpoint was massive haemorrhage, and secondary endpoints included compound myocardial infarction, stroke, cardiovascular death, venous thromboembolism, cardiovascular hospitalization and all-cause death.

The results of the COMPASS study showed that for patients with coronary heart disease and PAD who did not need dual antiplatelet therapy, combined application of the new anticoagulant rivaroxaban and aspirin was significantly better than aspirin alone in preventing cardiovascular events and could further reduce the risk of residual cardiovascular events in this high-risk group. The subgroup analysis results showed that combined application of rivaroxaban and aspirin could reduce stroke by 42% compared with aspirin alone. Therefore, new and more specific measures of oral anticoagulation combined with aspirin to prevent stroke are expected to be obtained through subgroup analysis, and the study conclusion needs further tests to confirm.

Recommendations

[1] For patients with symptomatic intracranial artery stenosis, antiplatelet therapy should be started as soon as possible and used long term. The alternative antiplatelet drugs are aspirin, clopidogrel, and cilostazol. (Class I, Level of Evidence A).

[2] Minor stroke patients with high-risk intracranial artery stenosis (70% to 99%), was treated with single antiplatelet therapy after 90 days of dual antiplatelet therapy (aspirin and clopidogrel), and combined stent therapy was not recommended. (Class III, Level of Evidence B).

[3] For stroke patients with intracranial arterial stenosis, aspirin plus clopidogrel is recommended to reduce the risk of early stroke recurrence caused by

thromboembolism. One week later, the risk is reassessed for the purpose of determining whether to continue the combined treatment. The duration of dual antiplatelet therapy can last for 3 months after the onset of the disease. Routine anticoagulant therapy is not recommended for secondary prevention (Class I, Level of Evidence A).

(2) Surgical intervention: combined intracranial and extracranial macrovascular stenosis and hemodynamic mechanism

1. Carotid endarterectomy The safety of emergency CEA is still uncertain. An observational study included 369 stroke patients with CEA operation interval ≤ 1 week. The results suggested that early CEA operation after stroke was feasible and relatively safe [519]. A study enrolled a total of 193 patients who underwent CEA due to symptomatic stenosis, including 90 AIS patients and 27 TIA patients. The results suggested that patients undergoing emergency CEA surgery had a higher risk than selected patients undergoing CEA surgery [520]. Another study included 3023 patients with carotid artery stenosis, 176 of whom underwent CEA within 48 hours due to acute progressive stroke or transient ischemic attack. This study suggested that the risk of CEA within 48 hours of onset for selected patients with progressive stroke or TIA was within an acceptable range, and the benefit of CEA for symptomatic patients at an early phase was to prevent recurrence of stroke [521].

Paty et al's[522]study showed that for patients with infarct size larger than 1cm in

diameter, the risk of permanent neurological impairment after CEA increased by 1.7 times. Therefore, early CEA may be suitable for mild and non-disabling stroke, and its purpose is to reduce continuous thromboembolism or flow-restrictive ischemia. The results of this study also suggested that the incidence rate of postoperative stroke deterioration and the postoperative results of CEA patients were similar and acceptable within one month of stroke, and it is considered that surgery at any time within one month after stroke onset is feasible.

Recommendations

[1] When clinical indicators or brain imaging demonstrate that the core of small infarction and at risk area (penumbra) are caused by insufficient blood flow due to severe stenosis or occlusion of the carotid artery, or acute neurological impairment after CEA with suspected acute thrombosis at the site of operation, the effectiveness of emergency CEA has not been confirmed (Class II, Level of Evidence B).

[2] The effectiveness of emergency CEA has not been proven in patients with unstable neurological status (such as progressive stroke) (Class II, Level of Evidence B).

2. Other surgical treatment A study in 2013 included only 20 AIS patients due to cerebrovascular atherosclerosis. Superficial temporal artery-middle cerebral artery

(STA-MCA) bypass surgery was given within 7 days after symptoms appeared. Results suggested that early bypass surgery was safe and effective, and some of the patients showed rapid improvement of neurological function. Therefore, some selected AIS patients with small infarcts visible on imaging may benefit from early STA-MCA bypass surgery [523].

Intracranial and extracranial vascular bypass surgery for the treatment of ischemic stroke is considered ineffectual. Little literature has reported the benefits of early bypass surgery, nor did they report haemorrhagic complications. Intravascular therapy seems to be a better choice in most cases.

II. Management of cardiogenic stroke

(1) Anticoagulation treatment initiation

Cardiogenic stroke is the most common and serious type of stroke besides atherosclerosis. For the treatment of cardiogenic stroke, besides actively treating primary heart condition, anticoagulant therapy should be started based on the situation to prevent stroke recurrence.

The study "Heparin in Acute Embolic Stroke Trial" (HAEST) is the only RCT study to research the timing of anticoagulation. The results showed that patients without high risk factors of haemorrhage had a low risk of haemorrhage when low molecular weight heparin (LMWH) or aspirin was applied within 30 hours. The European Atrial Fibrillation Trial (EAFT) showed that anticoagulation therapy was effective within 14 days after onset [524]. ACCP recommended in 2012 that anticoagulation therapy should

be started within 2 weeks for patients with non-large cerebral infarction and cardiogenic embolism without other haemorrhagic risks. For patients with a high risk of bleeding, large infarct area or poor blood pressure control, the anticoagulation time should be extended to later than 14 days [567].The HAS-BLED score can be used to predict bleeding risk of patients undergoing anticoagulant therapy, and patients with a total score of ≥ 3 points are regarded as high-risk patients prone to haemorrhagic transformation.

For new oral anticoagulants, their anticoagulant effects should not be inferior or superior to warfarin, and their cerebral haemorrhage complications should be less than that of warfarin, with high safety. Some foreign studies suggest that the size and severity of infarct lesion should be taken into account when anticoagulation is considered, suggesting that anticoagulation treatment can be initiated one day after TIA. Non-disabling small-area infarction should be anticoagulated 3 days after onset and moderate-area infarction should be anticoagulated 6 days after onset. However, massive infarction should be anticoagulated at least 2-3 weeks after onset [525].

Atrial fibrillation is the most common cause of cardiogenic stroke. A multicentre retrospective cohort study included 1,029 AIS patients newly diagnosed with atrial fibrillation. Anticoagulant therapy was initiated within 4-14 days after stroke, showing a better 90-day composite outcome, including stroke, TIA, systemic embolism, symptomatic intracranial haemorrhage and severe extracranial haemorrhage (comparation between anticoagulation initiated 4-14 days after stroke

and within 4 days, *HR*=0.53, 95% *CI:* 0.30~0.93). High CHADS2-VASC score, high NIHSS score, large infarct size and anticoagulation type were associated with adverse outcomes [526]. A retrospective, open-label study included 60 patients with atrial fibrillation and mild to moderate AIS (NIHSS < 9), suggesting that patients treated with rivaroxaban within 14 days after onset had no symptomatic haemorrhage within 7 days after anticoagulation was initiated [527].

Recommendations

[1] For patients with non-massive cerebral infarction and not from cardiogenic embolism and without other bleeding risks, anticoagulant therapy is recommended and to be initiated within 2 weeks (Class IIa, Level of Evidence B).

[2] For patients at high risk of bleeding, or large infarction area or poor blood pressure control, the timing of initiation of anticoagulation therapy should be extended to beyond 2 weeks (Class IIa, Level of Evidence B).

[3] The size and severity of stroke should be taken into account when consider anticoagulation. It is suggested that anticoagulation can be initiated 1 day after TIA, 3 days after non-disabling small infarction, and 6 days after moderate size infarction. Large area infarction should wait at least 2 to 3 weeks (Class IIa, Level of Evidence B).

[4] For most AIS patients with atrial fibrillation, it is reasonable to start oral anticoagulant therapy within 4 to 14 days after onset (Class IIa, Level of

Evidence B).

(II) Drug selection

1. Oral anticoagulant Warfarin has definite therapeutic value in primary prevention[528] and secondary prevention[524] of stroke in patients with atrial fibrillation. The best dosage of warfarin anticoagulant therapy is when INR value is of 2.0-3.0, which gives due consideration to the curative effect and bleeding risk [529]. For patients with atrial fibrillation who still suffer from ischemic stroke or TIA after anticoagulant therapy, there is no evidence to support the prevention of ischemic events by increasing drug dosage.

The new oral anticoagulants are convenient to take, do not require adjustment of the dosage or frequent monitoring of the INR value, and have clear benefits and low bleeding risks for patients with non-valvular atrial fibrillation. These anticoagulants have been recommended by the guidelines of various countries in recent years. Several RCT studies have verified the efficacy and safety of dabigatran, rivaroxaban, apixaban and edoxaban in preventing stroke and embolism events in patients with atrial fibrillation [530-534]. New oral anticoagulants provide a new choice for prevention of thromboembolic complications in patients with atrial fibrillation. However, due to limited application time and clinical experience in China, it is still difficult to be widely used, therefore warfarin is still the preferred oral anticoagulant. The 2016 Canadian Guidelines for Atrial Fibrillation Management emphasizes that warfarin,

instead of new oral anticoagulant drugs, should be the first choice for patients with mechanical valves, rheumatic mitral stenosis and glomerular filtration rate of 15-30 ml/(min·1.73m^2) with indications of oral anticoagulants [567].

Recommendations

[1] For ischemic stroke or TIA patients with atrial fibrillation (including paroxysmal), appropriate doses of warfarin are recommended to prevent the recurrence of thromboembolism. The target dose of warfarin is to maintain INR at 2.0 to 3.0 (Class I, Level of Evidence A).

[2] New oral anticoagulants can be used as an alternative to warfarin. New oral anticoagulants include dabigatran, rivaroxaban, apixaban and edoxaban (Class I, Level of Evidence A). Individual factors should be taken into account in the selection of drugs.

2. Heparin AIS has been treated by intravenous application of anticoagulants for more than 50 years, but this have become less common. Reasons to use such anticoagulants for acute stroke include: ① prevent aggravation of neural function; ② prevent early embolism recurrence; and ③ improve neural outcome[535-536] The previous AHA expert consensus considers that the results of safety and effectiveness of heparin or other anticoagulants administrated during acute phase are negative or uncertain [537-539]. Other investigators also believe that the available clinical trial data

cannot support the effectiveness of emergency anticoagulation in the treatment of recurrent ischemic stroke [540-541]. Two Meta analyses also verify that the emergency anticoagulation is lack of benefit [542-543]. Another non-blind RCT study not included in the two Meta analyses compared the efficacy of low molecular heparin (LMWH) and aspirin on prevention of early neural function aggravation. Though LMWH was superior than aspirin in subgroups based on age (LMWH, 63.82% vs Aspirin 44.63%; $P<0.001$) and posterior infarction (LMWH, 75.19% vs Aspirin 40.48%, 0<0.001), the difference was not significant for subgroups analysis of aaetiology, sex, NIHSS score, and anterior infarction [544].

In a random, double-blind placebo control test using danaparoid intravenously, the subgroup analysis for different pre-set subtypes of patients showed that only the patients with stenosis > 50% due to aortic atherosclerosis benefited from the treatment, specifically, 53.8% of patients in the danaparoid group compared to 38.0% of patients in the placebo group achieved good outcome at 7d ($P = 0.023$) [545]. The result is consistent with the result of early recurrence rate of stroke patients due to serious atherosclerosis found in other studies [546]. A random test conducted in Singapore and Hong Kong compared Asian patients taking aspirin or nadroparin within 48h of onset for aortic atherosclerotic stroke. Almost all patients had serious stenosis or intracranial artery occlusion, and there were a few patients with extracranial arterial disease. The test showed that there was no significant difference in either haemorrhage or clinical benefit [547]. A multicentre study discussed the

efficacy of subcutaneous injection of enoxaparin or dose-adjusted unfractionated heparin in the highly stenosis or cardioembolic stroke patients, and no significant difference was found [548].

The optimal pharmacotherapy is still uncertain for AIS patients with imaging evidence of nonocclusive intraluminal thrombosis (such as carotid artery and vertebrobasilar artery). Several small observation studies confirmed the safety of short-term intravenous infusion of heparin or LMWH in such population [549-550]. More studies are needed to be verified of its effectiveness and safety.

Recommendations

[1] Emergency anticoagulant therapy for AIS patients is not recommended for the prevention of early recurrence of stroke, stop the deterioration of neurological function and improve the outcome of AIS (Class III, Level of Evidence A).

[2] The effectiveness of emergency anticoagulant therapy is unclear in AIS patients with severe ipsilateral internal carotid artery stenosis (Class IIb, Level of Evidence A).

[3] For AIS patients with extracranial intravascular non-occlusive thrombosis, the safety and efficacy of short-term anticoagulant therapy are unclear (Class IIb, Level of Evidence C).

(III) Aaetiology management

1. Atrial fibrillation One of the important complications of atrial fibrillation is cardiogenic brain embolism. The studies show that oral administration of warfarin can effectively prevent ischemic stroke [567] in atrial fibrillation patients, and the risk of stroke is reduced by more than 60% [583]. Therefore, theroretically, in absence of contraindications, all atrial fibrillation patients having had stroke attack shall take anticoagulants for a long term. However, in the clinical practice, warfarin is desperately underused by atrial fibrillation patients [567], and the treatment rate with warfarin for ischemic stroke patients with atrial fibrillation in China is only 16.2% [528].

A meta-analysis shows aspirin alone is effective for ischemic stroke or TIA patients with atrial fibrillation if failing to take anticoagulants orally [551]. Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-A) verified the benefits of a combination of aspirin and clopidogrel in atrial fibrillation patients non-applicable for anticoagulation, however with increased risk of haemorrhage[552]. The ACTIVE-W study confirmed the advantage of anticoagulation over dual antiplatelet therapy in atrial fibrillation patients [553]. The EAFT study also confirmed the advantage of anticoagulation over dual antiplatelet therapy in TIA or mild stroke patients with atrial fibrillation [524].

In China, the incidence of atrial fibrillation is 11.45% in the initial ischemic stroke or TIA patients, which is significantly lower than the incidence in foreign countries (17.8-24.6%), showing low detection rate of atrial fibrillation in the ischemic stroke or TIA patients in China. Newly developed atrial fibrillation is detected in about 10%

of ischemic stroke or TIA patients during admission by the current conventional examination means (routine ECG or 24h ECG). The Stroke and Monitoring for PAF in Real Time (SMART) study adopted a consecutive 30d ECG monitoring, which can increase the detection rate of atrial fibrillation by 11% [554]. Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) included cryptogenic ischemic stroke or TIA patients without atrial fibrillation as verified by routine 24h dynamic ECG monitoring as the study population, compared the detection rates of paroxysmal atrial fibrillation between 30d ECG monitoring and repeated 24h dynamic ECG monitoring, and showed that only 4% of atrial fibrillation was found in the repeated 24h dynamic ECG monitoring records, 20% in 30d ECG records. The detection rate of atrial fibrillation may be increased by prolonging the ECG monitoring time, which is of great importance for the cardiogenic embolism caused by atrial fibrillation [555].

Recommendations

[1] For ischemic stroke or TIA patients with atrial fibrillation, the time of anticoagulation should be chosen according to the severity of ischemia and the risk of bleeding transformation. It is suggested that anticoagulation therapy should be given within 14 days after the onset of neurological symptoms to prevent stroke recurrence. For patients with high risk of bleeding, the timing of anticoagulation should be appropriately prolonged (Class IIa, Level of Evidence B).

[2] If ischemic stroke or TIA patients with atrial fibrillation are unable to receive

oral anticoagulant therapy, aspirin alone may be considered for treatment (class IIa recommended, class B evidence). Aspirin combined with clopidogrel should be carefully selected and antiplatelet therapy (Class IIb, Level of Evidence B).

2. Other cardiogenic embolisms Ischemic stroke following acute myocardial infarction is one of the exocardial complications of myocardial infarction. Left ventricular mural thrombosis easily occurs due to massive myocardial infarction, particularly in anterior myocardial infarction with apex involvement. Anticoagulation should be taken into consideration to prevent thrombosis development if the patient has low haemorrhagic risks. Mural thrombosis, once diagnosed, shall be treated with oral administration of vitamin k antagonist. If stenting and dual antiplatelet therapy have been performed, the addition of oral administration of anticoagulants may increase the haemorrhagic risks of patients. Therefore, anticoagulation plus dual antiplatelet therapy may only be used for ST-segment elevation myocardial infarction patients whose risks of systemic circulation embolism or venous thromboembolism are higher than the haemorrhagic risks. When triple antithrombotic therapy is needed, the range of INR should be controlled to be 2.0-2.5.

Valvular heart diseases (mitral stenosis, mitral annulus calcification, mitral regurgitation, mitral prolapse, aortic valve disease, heart valve prosthesis and biovalve) may also increase the risk of cerebrovascular disease events caused by cardiogenic embolism. Antithrombotic therapy for valvular heart diseases is of great significance for reducing thrombosis. However, the possible increase of haemorrhagic

risk must be taken into account. Therefore, antithrombotic therapy should be used to maintain the best balance between thrombosis and haemorrhagic risk [567]. In summary, patients with cardiogenic embolic stroke due to heart diseases shall seek medical advices in the cardiology department as early as possible.

The incidence of patent foramen ovale is 15-25% in adults, and the incidence of atrial septal aneurysm is 1-4%. A right-to-left shunt channel may be formed due to patent foramen ovale, resulting in paradoxical embolism from the venous system, while atrial septal aneurysms easily result in thrombosis. Patent foramen ovale and atrial septal aneurysms are associated with the stroke in many but not all studies [556-564]. In the PICSS study, it was shown through transoesophageal ultrasound scan that the incidence of patent foramen ovale was higher in the patients with cryptogenic stroke than in patients with stroke due to known reasons (39.2% *vs.* 29.9%)[557, 565] However, not all of the stroke patients with patent foramen ovale have paradoxical embolism from deep venous system. It's suggested that the cryptogenic stroke patients with patent foramen ovale should undergo Doppler ultrasound scan for veins in lower limbs to exclude the deep venous thrombosis. The incidence of deep venous thrombosis in stroke patients is about 7.6%. Routine pelvic MR venography remains to be discussed for screening of cryptogenic stroke [565].

RESPECT study included 980 PFO patients, with median follow-up time of 5.9 years. RESPECT study showed that the risk of stroke recurrence after PFO occlusion by Amplatzer PFO occluder (Abbott vascular, former St.Jude medical) was reduced[566].

The REDUCE study was one of the first studies to use Helex (Gore＆Associates) and

Cardioform ventricular septal occluders (Gore＆Associates). It compared patients undergoing closure therapy and long-term antiplatelet therapy with the patients undergoing antiplatelet therapy alone. REDUCE study included 664 patients, median follow-up time was 3.2 years. Results indicated PFO occlusion patients had obvious clinical benefits [567]. The two studies above show that PFO occlusion therapy indeed reduces the risk of recurrent ischemic stroke, and that PFO occlusion related risk is very low.

Recommendations

[1] In ischemic stroke or TIA patients with acute myocardial infarction, and left ventricular mural thrombus, warfarin oral anticoagulation therapy is recommended for at least 3 months (target INR = 2.5, range 2.0 to 3.0) (Class IIa, Level of Evidence B).

[2] If there is no left ventricular mural thrombus, but no movement or abnormal movement of the anterior wall is found, oral anticoagulation therapy of warfarin for 3 months should also be considered (target INR value = 2.5, range 2.0 to 3.0) (Class IIa, Level of Evidence B).

[3] For ischemic stroke or TIA patients with rheumatic mitral valve disease but without atrial fibrillation and other risk factors, such as carotid stenosis, oral anticoagulation therapy with warfarin is recommended (target INR = 2.5, range 2.0 to 3.0) (Class IIa, Level of Evidence B).

[4] Patients with rheumatic mitral valve disease who have been treated with warfarin, routinely combining with antiplatelet therapy after ischemic stroke or TIA is not recommended (class III recommended, class C evidence). However, aspirin antiplatelet therapy can be added when ischemic stroke or TIA still occurs during the treatment of sufficient amount of warfarin (Class IIa, Level of Evidence B).

[5] Ischemic stroke or TIA patients with non-rheumatic mitral valve disease or other valve diseases (local aortic arch, mitral annulus calcification, mitral valve prolapse, etc.) without atrial fibrillation may consider antiplatelet therapy (Class IIa, Level of Evidence B).

[6] For patients with ischemic stroke or TIA and mechanical artificial heart valve, long-term warfarin oral anticoagulation therapy is recommended (INR 2/5-3.5) (Class IIa, Level of Evidence B).

[7] For patients with previous history of ischemic stroke or TIA and mechanical artificial heart valves, if the risk of bleeding is low, aspirin can be used in addition to warfarin anticoagulation (Class IIa, Level of Evidence B).

[8] It is suggested that any decision on PFO occlusion should be made jointly by neurologists and cardiologists (Class I, Level of Evidence A).

[9] Before PFO occlusion, other known causes of ischemic stroke (including monitoring arrhythmias) should be carefully excluded. The possibility of PFO correlation with the stroke, risk factors, and lifestyle changes should be assessed.

And communication between patients and multidisciplinary clinical teams should be involved in making the decision. For ischemic stroke caused by PFO, PFO occlusion can be performed to reduce the risk of stroke recurrence (Class I, Level of Evidence A).

III. Small vessel disease

Lacunar infarction caused by cerebral small vessel disease accounts for 25-50% of ischemic stroke, while the recurrence rate of stroke caused by small vessel disease is slightly lower than that of stroke caused by great vessel atherosclerosis. Cerebral arteriolar hyaline degeneration or amyloidosis has different pathological changes compared to atherosclerosis, and antithrombotic therapy on this population may have poorer efficacy than that of large arterial stroke. A single antiplatelet agent, including aspirin, clopidogrel, and cilostazol, should be administrated as secondary prevention for newly-developed symptomatic subcortical small infarctions. Several studies show that long-term administration of a combination of two antiplatelet agents will increase the risk of cerebral haemorrhage, which causes the disadvantages to outweigh advantages. SPS3 study showed dual use of aspirin and clopidogrel could not reduce the recurrence risk of stroke, but increased the risk of cerebral haemorrhage as compared with aspirin alone[140]. Many patients with symptomatic subcortical small infarction may have concurrent multiple lacunar infarction, white matter hyperintensities and microbleeding, increasing the risk of haemorrhage. For those

patients, cilostazol can be chosen if antiplatelet therapy is needed.

The occurrence and development of age and vascular risk factor related small vessel disease are very closely associated with hypertension. Elevated systolic and diastolic arterial pressure is an independent risk factor for the occurrence and development of cerebral small vessel disease. However, it's not enough to control the systolic pressure and diastolic pressure in normal ranges. High fluctuation of blood pressure will also accelerate development of the small vessel disease. The hypertensive cerebral haemorrhage is usually accompanied with drastic fluctuation of blood pressure before attack. Too high blood pressure variability will promote the progress of cerebral small vessel disease. The standard deviation of change in systolic or diastolic pressure, coefficient of variation and mean-independent variation may be used as parameters to evaluate the variability of blood pressure. Ideal blood pressure fluctuation range is yet unknown. However, we should pay attention to blood pressure variability during visits in addition to control of systolic and diastolic pressure. Increases blood pressure variability is an independent risk factor of development of cerebral microbleeding. Too high or too low blood vessel change will aggravate the clinical symptoms of cerebral small vessel disease, causing dizziness, instability of gait or vascular cognitive function decline, and even result in cerebral haemorrhage or lacunar infarction.

Recommendations

[1] The mechanism of ischemic stroke caused by small vascular disease is complex. At present, it is recommended to manage blood pressure, and use of aspirin, or clopidogrel or cilostazol (Class I, Level of Evidence B).

[2] Cerebral small vessel disease leads to a significant decrease in the adaptability of brain tissue to the changes of excessive hypertension and hypotension. The blood pressure of patients should be closely monitored (Class IIa, Level of Evidence B).

[3] Control of systolic and diastolic pressure is the key factor to control the incidence and progression of cerebral small vessel disease (Class IIa, Level of Evidence B).

[4] It is necessary to monitor the 24-hour ambulatory blood pressure in patients with cerebral small vessel disease. When conditions permit, it is best to detect changes in blood pressure during head upright tilt test (Class I, Level of Evidence B).

IV. Management of stroke due to special aaetiology

(I) Aortic dissection

CADISS study team published a random, open-label, phase II anticoagulation vs. antiplatelet feasibility trial, which enrolled 250 patients with extracranial carotid artery or vertebral artery dissection from 46 centres in UK and Australia[568]. The primary outcome was ipsilateral stroke or all-cause death 3 months after

randomization by intention to treat analysis, and there was no significant difference between both groups. There was also no difference in serious haemorrhage rate. The event incidences of both groups were low in the phase II clinical trial, therefore the phase III clinical trial might not be carried out. The limitations of the study also include lack of central imaging data in 20% of cases, and mean randomization time of 3.65 days, which is not enough to cover the hyperacute cases. Nonetheless, CADISS study confirmed the conclusion of many previous observational studies, i.e., no significant difference between the carotid artery dissection patients treated by anticoagulation and antiplatelet therapy. In addition, the follow-up analysis found no difference in the natural history of dissecting aneurysm and relevant stroke risk between two treatment groups, showing the overall prognosis was good [569].

(II) Moyamoya disease and moyamoya syndrome

Moyamoya disease is a cerebrovascular disease featured by chronic progressive stenosis or occlusion of bilateral terminal internal carotid arteries, anterior cerebral artery or middle cerebral artery, with secondary abnormal vessel network. Moyamoya disease and moyamoya syndrome have complex and various clinical manifestations. Cerebral ischemia is most common, manifested as transient ischemic attack (TIA), reversible ischemic neurologic deficit (RIND) or cerebral infarction. TIA is usually induced by emotional stress, crying, strenuous exercise or eating of hot spicy food. For moyamoya disease, angiography is a gold standard for diagnosis. HR-MRI is also of some help to the diagnosis of moyamoya disease. Willis circle proximal aorta

involvement is most bilateral; decrease of external diameters of vessels, generally without positive remodelling; obvious vascular wall thickening, obvious luminal stenosis; mild concentric strengthening, irrelevant to symptoms, generally no inflammatory cell infiltration on pathological examination. There's no definitely effective drug for moyamoya disease at present. A major therapy for moyamoya disease and moyamoya syndrome is extracranial-intracranial vascular reconstruction, which can effectively prevent and treat ischemic stroke.

(III) Vasculitis due to various reasons

Its incidence is low at only 2.4/1 million persons·year. It is classified as primary vasculitis and secondary vasculitis (autoimmune/infectious), and should be diagnosed and treated early. Diagnosis criterion of primary central nervous system vasculitis: acquired or other unexplainable neural or mental abnormality; vasculitis verified by angiography or tissue biopsy; no other evidence of secondary vasculitis. Brain tissue biopsy has low sensitivity (less than 50%), and is invasive, while the angiography (for luminal stenosis, tumour-like dilation and beaded change) has low specificity.

On HR-MRI, vasculitis has the following imaging characteristics: vascular distribution - intracranial artery and arteriole with diameter of 100-500μm, intracranial proximal aorta and multiple vessels can also be involved; vessel wall thickening - mainly concentric thickening, less eccentric thickening, the same signal as grey matter on T_2WI; vascular wall strengthening - uniform, smooth and concentric, associated with inflammation activity level, strengthening degree may be

reduced by hormonotherapy; vascular wall strengthening may vary during follow-up, but luminal stenosis generally has little change, and its recovery period is long. Thickening and strengthening of vascular wall of vasculitis patient; sustained stenosis may be seen after follow-up for 3 months. If diagnosed with central nervous system vasculitis, the patients shall receive hormonotherapy or immunosuppressor treatment.

(IV) Cerebral venous system disease

Venous infarction is derived from venous sinus thrombosis, cortical venous thrombosis and deep venous thrombosis. Venous infarction is mainly featured by noncompliance with arterial blood supply distribution region and high probability of haemorrhage, mainly vasogenic ooedema (as compared to cytotoxic ooedema). High density is shown on CT for small venous thrombosis. MR manifestations depend on the blood composition, but there should be no flow void effect in any case. Deep venous thrombosis is usually manifested as unilateral or bilateral (more common) thalamic oedema (thrombosis in internal cerebral vein). Venous infarction is mainly featured by severe cerebral oedema and haemorrhage. Sometimes it causes idiopathic intracranial hypertension and does not result in brain parenchyma injury. HR-MRI can be also used for evaluating the intracranial venous conditions of such patients.

Recommendations

[1] For ischemic stroke patients with defined aetiology, targeted etiological treatment is needed (Class I, Level of Evidence A).

[2] For AIS patients with extracranial carotid or vertebral artery dissection, antiplatelet or anticoagulant therapy for 3 to 6 months may be reasonable (Class IIa, Level of Evidence B).

[3] For patients with moyamoya disease and smoke syndrome, it is suggested that active drug treatment should be taken for underlying diseases or complications, and the risk factors of stroke should be effectively controlled and managed. It is necessary to choose the appropriate time and mode of operation according to the evaluation of patients (Class IIa, Level of Evidence B).

[4] The diagnosis of vascular inflammatory diseases in the central nervous system is difficult, and the etiological treatment should be carried out on the basis of definite diagnosis (Class IIa, Level of Evidence B).

[5] For patients with suspected venous cerebral infarction, it is suggested to complete intracranial venous system angiography. After that, according to the clinical and imaging results, these patients will receive etiological and symptomatic treatment (Class IIa, Level of Evidence B).

Section 9 Management of risk factors and long-term intervention

I. Blood pressure management

Hypertension is the most important risk factor of stroke and TIA. The diagnosis rate of hypertension in the patients with the attack of ischemic stroke recently is as high as 70% [329, 596]. The blood pressure management post stroke is an issue of concern. There are many disputes on the initiation opportunity of antihypertensive therapy and target blood pressure.

(I) When to initiate antihypertensive therapy

Several clinical random control studies including PRoFESS, ACCESS and SCAT studies, and meta-analysis consistently show it's safe to initiate the antihypertensive therapy within 48-72h after the occurrence of an AIS event, but the improvement of functional prognosis or decrease of mortality is not definite [570]. An ongoing China Antihypertensive Trial in Acute Ischemic Stroke II (CATIS-2) initiated in 2017 will explore the efficacy of antihypertensive therapy within 24-48h after AIS, and is intended to test if the risk of death and serious disability can be reduced by early antihypertensive therapy within 24-48h after AIS as compared to delayed antihypertensive therapy (7d after attack).

Another question as to when to initiate the antihypertensive therapy is: whether hypertensive patients previously taking anti-hypertensive drugs shall stop or continue taking anti-hypertensive drugs in the acute phase of ischemic stroke? COSSACS and ENOS studies answer this question. Both of these trials point out that the patients

cannot benefit from the administration of hypotensive drugs in the acute phase of ischemic stroke, but it does not result in aggravation or poor prognosis [571]. China Guideline for Secondary Prevention of Ischemic Stroke and Transient Cerebral Ischemic Attack 2014 points out that the antihypertensive therapy shall be restarted several days after attack for the ischemic stroke or TIA patients having hypertension history and taking hypotensive drugs for a long term in case of no absolute contraindications [572].

A large sample size random prospective study showed the antihypertensive therapy within 24 could not improve the 14d disability rate or death rate [573]. Later, the study found antihypertensive therapy initiated within 24-48h after the ischemia event could improve the clinical prognosis at 3 months and reduce the recurrence and death rates [574]. In addition, a large sample size random control study with follow-up for 6 months showed that the higher baseline blood pressure or high blood pressure variation within 24h was associated with poor prognosis, but the prognosis could be improved by antihypertensive therapy within 24h [575]. Patients under thrombolysis have better prognosis if their blood pressure is controlled < 160mmHg as compared with the patients whose blood pressure is > 160mmHg, the patients whose blood pressure is controlled < 140mmHg have better prognosis than above mentioned patients[576], and many studies support that the patients may benefit from the early blood pressure control (140-160)/(80-99)mmHg after stroke [577-578].

However, a study and 2 meta analyses show that the hypotensive drugs can effectively

lower the blood pressure at the acute phase, but have no influence on the short-term and long-term prognosis and death rate [579-583]. Relatively small sample size random control studies also find that antihypertensive therapy has no obvious influence on the prognosis [584], but may increase the risk of early neurological deterioration [471-472, 585-586]. A study shows that the antihypertensive therapy possibly has different influence on prognosis according to different types of stroke [587].

(II) Management target of blood pressure during acute phase

1. For the general population The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) observed 4071 ischemic stroke patients at acute phase (within 24h after admission) within 48h after ischemic attack. The influence of intensified antihypertensive therapy on death and serious disability at 14d, during discharge and at 3 months in the patients whose blood pressure was above 140/90mmHg was analysed, showing that the patients in the intensified antihypertensive therapy group did not obviously benefit from it, but it might be safe to control the blood pressure below 140/90mmHg [557].

There's no definite study conclusion on the control target of blood pressure from which the patients may get maximum benefits after AIS. Some observation studies confirmed that lower blood pressure was associated with poor prognosis after stroke, but this conclusion is disputed in different studies [473, 588-594]. There's no study on the hypotension treatment for stroke patients. A meta-analysis including 12 studies compared the influence of crystalloid solution and colloidal solution on prognosis,

showing that the death rates and disability rates were similar. There's no definite study data which may be used to instruct the dose and application duration of such expansion solutions [595]. There's no study comparing the expansion effects of different isotonic fluids. There's no definite study result on the treatment significance of drug-induced hypertension among AIS patients.

Recommendations

[1] For patients with blood pressure < 220/120 mm Hg, who do not receive IV rt-PA or endovascular treatment and do not have complications requiring emergency antihypertensive treatment, starting or restarting antihypertensive therapy within the first 48 to 72 hours after AIS is not effective in preventing death or severe disability (Class III, Level of Evidence A).

[2] For patients with blood pressure ≥ 220/120 mm Hg, who do not receive IV rt-PA or endovascular treatment and do not have complications requiring emergency antihypertensive treatment, the effect of starting or restarting antihypertensive therapy within the first 48 to 72 hours after AIS is uncertain. It may be reasonable to reduce blood pressure by 15% within the first 24 hours after a stroke attack (Class IIb, Level of Evidence C).

2. Special populations (Patients with ICAS, medical complications, and blood pressure > 220/110mmHg) AIS patients may have other serious comorbidities, and

emergency antihypertensive treatment needs to be initiated to prevent more serious conditions. However, in some cases, excessively rapid blood pressure reduction may lead to aggravation of intracranial ischemia [505], so antihypertensive treatment needs to be vigilant. In this case, the ideal antihypertensive treatment should be to achieve an overall antihypertensive effect of 15% through individualized treatment.

Patients with very high blood pressure (blood pressure > 220/120mmHg in general) have been excluded in existing studies [557, 596-600]. Therefore, for these patients, the antihypertensive effect has not been clearly demonstrated in the absence of a clear medical complication.

Recommendations

[1] For AIS patients with other complications (such as simultaneous acute coronary events, acute heart failure, aortic dissection, bleeding transformation after thrombolysis, or preeclampsia/eclampsia), early antihypertensive therapy is indicated. At the initial stage, a 15% reduction in blood pressure may be safe (Class I, Level of Evidence C).

[2] Hypotension and hypovolemia must be corrected after stroke to ensure systemic perfusion to support organ function (Class I, Level of Evidence C).

[3] For AIS patients, the therapeutic effect of drug-induced hypertension is uncertain (Class IIb, Level of Evidence C).

(III) Antihypertensive target level in secondary prevention of hypertension

In the Post-Stroke Antihypertensive Treatment Study (PATS) conducted in China to investigate the effectiveness of antihypertensive treatment in secondary prevention of hypertension, 5,665 patients with recent TIA or minor strokes (haemorrhagic and ischemic) were selected and randomly divided into indapamide treatment group and placebo group. The results after an average follow-up time of 24 months indicated that the recurrence rate of stroke in the indapamide group was significantly lower than that in the placebo group (30.9% *vs.* 44.1%), and the relative risk of stroke recurrence was reduced by 30% [601]. The early Perindopril Protection Against Recurrent Stroke Study (PROGRESS) has once again confirmed the effectiveness of blood pressure control in secondary prevention of stroke [602]. A meta-analysis conducted in 2009 has demonstrated that antihypertensive treatment can significantly reduce the recurrence risk of stroke and TIA, and the greater the reduction in systolic blood pressure, the more significant the effect of reducing the risk of stroke recurrence [603].

Both clinical trials have demonstrated that initiating or continuing antihypertensive medication after hospitalization can improve the blood pressure management [604, 605]. For hypertension patients with stable neurological function during hospitalization, it is reasonable to initiate or restart antihypertensive treatment. These studies have evaluated patients with a previous history of hypertension. Since hypertension is commonly detected and diagnosed for the first time after admission to the hospital due to stroke, the above findings are still applicable to patients without a previous

history of hypertension. For patients with ischemic stroke or TIA induced by different causes, there is still no basis for determining the target value of hypotension. For patients with ischemic stroke or TIA due to atherosclerotic stenosis of intracranial artery (stenosis rate of 70% to 99%), systolic blood pressure is recommended to be reduced to less than 140 mmHg and the diastolic blood pressure to be reduced to 90 mmHg [606]. For patients with stroke or TIA due to low hemodynamic factors, the effect of blood pressure lowering velocity and amplitude on patients' tolerance and hemodynamic parameters should be weighed [607]. A total of 3,020 patients with lacunar infarction were included in the Secondary Prevention of Small Subcortical Strokes (SPS3) study, and randomly (non-blind) divided into two groups (Target systolic pressure < 130mmHg vs. 130-149 mmHg). Although there was no statistically significant difference in the risk of stroke recurrence between the two groups, the proportion of patients with cerebral haemorrhage in the group with systolic blood pressure < 130mmHg was drastically reduced, and the difference in the proportion of severe hypotension between the two groups was not statistically significant [608], which indicated that it may be more appropriate to control systolic blood pressure at < 130mmHg for patients with subcortical infarction that may be the cause of small vessel disease.

In the Systolic Blood Pressure Intervention Trial (SPRINT), the effects of intensive antihypertensive treatment (target value < 120mmHg) and standard antihypertensive treatment (< 140mmHg) on the risk of death and cardiovascular events were

compared [609]. The results indicated that the mean systolic blood pressure of patients in the intensive antihypertensive treatment group and the standard antihypertensive treatment group was 121.4 mmHg and 136.2 mmHg at 1 year, respectively. The annual rate of major composite endpoint events in the intensive antihypertensive treatment group was significantly lower than that in the standard antihypertensive treatment group (1.65% *vs.* 2.19%, $P< 0.001$). All-cause mortality was also significantly reduced in the intensive antihypertensive treatment group (risk ratio=0.73, $P=0.003$). However, the incidences of severe hypotensive adverse events, syncope, electrolyte abnormality, acute kidney injury or failure in the intensive antihypertensive treatment group were higher than those in the standard antihypertensive treatment group. Nevertheless, patients with diabetes, massive proteinuria, history of stroke, end-stage renal disease, recent acute coronary syndrome or patients hospitalized for heart failure, and other high-risk patients were all excluded from this study, so the conclusions cannot be simply generalized to all patients with hypertension.

The ACCORD study (Action to Control Cardiovascular Risk in Diabetes) in diabetic patients has found that strict antihypertensive treatment strategies cannot reduce patients' primary endpoint events but can significantly reduce the risk of stroke events [610]. The study believes that for diabetes patients, controlling systolic blood pressure to less than 130/80 mmHg may benefit patients more, but the conclusions of the study on patients with coronary heart disease, stroke, and chronic kidney disease are

unknown.

The ongoing Intensive Blood Pressure Intervention in Stroke Trial Sprint (IBIS) and China Antihypertensive Trial in Acute Ischemic Stroke II (CATIS-2) are conducted for further research on the target value of antihypertensive treatment in stroke patients.

Recommendations

If the patient has stable neurological function during hospitalization, but blood pressure > 140/90mmHg, it is safe to start or restart antihypertensive therapy. With the exception of contraindications, long-term control of blood pressure is reasonable (Class IIa, Level of Evidence B).

(IV) Selection of antihypertensive drugs

The benefit of antihypertensive treatment to reduce the risk of stroke mainly comes from antihypertension itself. Various commonly used antihypertensive drugs can be used as treatment options to control blood pressure in stroke patients. The RCT research evidence in the field of stroke should be combined with the pharmacological characteristics of different antihypertensive drugs and the individual situation of patients for appropriately chosen antihypertensive drugs. There is no precise data on the selection and dosage recommendation of antihypertensive drugs.

Recommendation

Although there is not sufficient data to guide the selection of antihypertensive drugs after AIS, the antihypertensive drugs and doses of figure 9 are reasonable. (Class IIa, Level of Evidence C).

II. Management of abnormal lipid metabolism

The study of Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) has shown that cholesterol level is one of the important factors for recurrence of ischemic stroke or transient ischemic attack (TIA). Cholesterol level lowering is important to reduce the recurrence of ischemic cerebrovascular disease and death. Intensive cholesterol-lowering regimen (80 mg of atorvastatin daily) can reduce the relative risk of stroke by 16% over 5 years [611]. Statins have a clear secondary preventive effect on stroke and have a certain effect in improving stroke prognosis.

(I) Time to start cholesterol-lowering treatment

In cases where blood cholesterol is not measured, statins may be recommended for patients with stroke which is presumed to be caused by atherosclerosis [660]. Measurement of blood cholesterol may be valuable for ischemic strokes that are presumed to be non-atherosclerotic, such as those caused by arterial dissection, because primary prevention guidelines for such strokes are made based on LDL-C levels [612].

There are only limited randomized controlled trials about early application of statins after AIS. In the study on rapid assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER), the effects of 40mg of simvastatin and placebo in the treatment of transient cerebral ischemia or mild stroke within 24h after attack were evaluated [661]. The trial was terminated early because of slow enrolment. There were no significant differences in recurrent stroke or safety endpoints between the simvastatin group and placebo group. The effectiveness of the FASTER study was insufficient due to early termination. The dose of statin used in this study was moderate (not high-intensity statins as recommended in secondary stroke prevention). When the application of statins started within 24 hours or within 7 days after attack, there was no difference in outcome after 90s. The ASSORT study (a statin study after AIS hospitalization) showed no difference in 90-day modified Rankin Scale (mRS) between the group initiating statins within 24 hours and the group initiating statins within 7 days [613].

Recommendations

[1] Routine measurement of blood cholesterol levels is not recommended for all patients with atherosclerotic ischemic stroke who are not on high intensity statins (Class III, Level of Evidence B).

[2] For patients with ischemic stroke during statins, it is reasonable to continue statins in the acute phase of stroke (Class IIa, Level of Evidence B).

[3] For patients who meet the requirements for statins, it is reasonable to start statins during the hospital stay (Class IIa, Level of Evidence C).

(II) Low density lipoprotein (LDL) target levels of cholesterol-lowering treatment after ischemic stroke

When the guideline development team reviewed randomized controlled trials on cholesterol management related to cerebrovascular disease and cardiovascular disease, no related records on the absolute target for low-density lipoprotein cholesterol (LDL-C) of 1.8mmol/L (or 70mg/dl) were found, but the target value of 2.6mmol/L or 1.8mmol/L was adopted in multiple observational studies or guidelines for reducing LDL-C [614-615]. The 2012 Canadian Cardiovascular Association Guidelines recommend that the lipid-lowering target for patients with cerebrovascular disease is set as LDL-C<2.0mmol/L or reduction of > 50% compared with baseline [616]. For high-intensity statin therapy, it is still recommended to use LDL-C<1.8mmol/L (70mg/dl) as the reference target value for cholesterol-lowering treatment in consideration of the content of international guidelines for cholesterol lowering and clinical practice in China. With respect to the treatment intensity of statins, it is defined as high-intensity statin therapy (intensive cholesterol lowering treatment) when the LDL-C value decreased by more than 50% compared with the baseline LDL-C value after treatment, and moderate-intensity statin therapy when there is 30% to 50% of decrease [612, 617].

Recommendations

It is suggested that LDL-C < 1.8mmol/L (70mg/dL) should be used as a reference target for cholesterol lowering therapy (Class IIa, Level of Evidence C).

(III) Patients who can significantly benefit from intensive cholesterol-lowering treatment

In the population with clinical atherosclerotic cardiovascular disease (ASCVD), patients with LDL-C of 190 mg/dl and above before treatment, 40-75 years old diabetes patients with LDL-C levels of 70-189 mg/dl without ASCVD, non-diabetes patients without ASCVD, but with a 10-year ASCVD risk ≥ 7.5% and LDL-C levels between 70 and 189 mg/dl are those who can benefit from cholesterol-lowering treatment the most [612].

As a study on non-cardiac ischemic cerebrovascular disease or TIA, patients with different etiological subtypes, ages, gender, baseline cholesterol levels, with or without carotid atherosclerosis and diabetes, and diabetes in subgroups of SPARCL study, all can benefit from intensive cholesterol lowering treatment [611], especially for subgroups with carotid atherosclerosis [618]. A subgroup analysis of stenting and intensive medical treatment in the prevention of recurrent stroke in patients with intracranial atherosclerosis (SAMMPRIS study) has indicated that intensive statin therapy should be used in stroke patients with intracranial atherosclerosis to prevent

stroke recurrence [619].

For ischemic stroke outpatients with atrial fibrillation, cholesterol-lowering treatment with statins can also reduce the recurrence rate [620].

High-intensity statin therapy or the combination treatment of statins with PSCK9 inhibitors can reduce the primary endpoint event rate (major vascular events, etc.) by 19% as compared with conventional-intensity statin therapy [621].

Recommendations

[1] Atrial fibrillation is not a reason for not using statins in patients with ischemic stroke (Class IIa, Level of Evidence B).

[2] High-intensity statins should be started or continued as a first-line treatment in female and ≤ 75-year-old male with ASCVD, unless there are contraindications (Class I, Level of Evidence A).

(IV) Cholesterol-lowering treatments other than statins

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new target for lipid-lowering therapy in recent years. PCSK9 monoclonal antibody (mAb) inhibitors can bind to the close region of the interaction site with LDLR in PCSK9, thus preventing PCSK9 from interacting with LDLR so that LDL-C can be cleared more by LDLR. Previous studies have demonstrated at the molecular level that inhibition of PCSK9 expression can effectively reduce LDL-C, and this effect is potent and profound. In

the FOURIER study (PCSK9 inhibitors in high-risk populations for further cardiovascular prognosis), 27,564 patients with atherosclerotic cerebrovascular disease, fasting LDL-C or non-HDL cholesterol elevation who received optimized lipid-lowering therapy (at least 20 mg of atorvastatin or other statins of equal strength) were randomly divided into subcutaneous evolocumab group or placebo group, with median follow-up time of 2.2 years. Evolocumab treatment significantly reduced composite primary endpoint events (cardiovascular death, myocardial infarction, stroke, hospitalization due to unstable angina pectoris, hospitalization for coronary recanalization) (9.8% *vs.* placebo group 11.3%; *HR*=0.85, 95% *CI:* 0.79-0.92); and could reduce composite secondary endpoint events (cardiovascular death, myocardial infarction or stroke) (5.9% *vs.* placebo group 7.4%; *HR*=0.80, 95% *CI:* 0.73-0.88) [622].

A meta-analysis including 23 randomized controlled studies has indicated that lipid-lowering treatment with niacin can't reduce cardiovascular death, disability, and non-disabling stroke [623]. A multi-centre, randomized, controlled, single-blind clinical trial conducted by domestic scholars has explored the treatment of AIS by reducing cholesterol levels via biofilm in combination with delipid extracorporeal lipoprotein filter (DELP), which has indicated that it can significantly improve neurological function and 90-day prognosis, especially in stroke patients with high blood lipid level, with no obvious adverse reactions [624].

Recommendations

In atherosclerotic ischemic stroke patients who have already optimized statins, measuring blood cholesterol levels may help identify those who can benefit from PCSK9 treatment (Class IIb, Level of Evidence B).

(V) Combined lipid-lowering treatment

There is no sufficient evidence for the effectiveness of monotherapy of ezetimibe or ezetimibe in combination with statins in the lipid-lowering treatment compared with statins. The transaminase test should be perfected before the application of ezetimibe, and the transaminase level should be monitored during application. If ALT continues to exceed the normal upper limit by 3 times, the application of ezetimibe should be discontinued. In the Study of Heart and Renal Protection (SHARP), 10mg of Ezetimibe in combination with 20mg simvastatin could reduce LDL-C levels by 23% in patients who received dialysis treatment and 33% in patients who didn't receive dialysis treatment compared with placebo [625]. In the study of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS), the incidence of composite endpoint events including ischemic stroke was not reduced in simvastatin + ezetimibe group compared with that in placebo group [626]. In the IM Proved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the incidence of composite events including ischemic stroke in patients with acute coronary syndrome in ezetimibe/simvastatin group was effectively reduced compared with that of placebo

/simvastatin group in the median 6-year long-term follow-up (the incidence of ischemic stroke decreased by 21%, *P*=0.008), which indicated that ezetimibe can effectively improve the prognosis of patients with acute coronary syndrome [627].

Recommendations

For patients with poor lipid-lowering effect or intolerable of statins, lipid lowering treatment can be combined with ezetimibe but regular monitoring of transaminase and physical examination should be done (Class IIb, Level of Evidence B).

See Supplemental Table 15 for the comparison table of doses of lipid-lowering drugs.

(VI) Instructors of statin cholesterol lowering treatment with statins and patient compliance

A study included secondary prevention of non-cardiac embolism ischemic stroke has indicated that although there is no difference in the overall incident rate 12-24 months after ischemic attack, the guidance group of specialists and nurses can better reduce lipid level, which is reflected in the reduction degree of LDL-C [628]. A meta-analysis based on observational studies has shown that the application of statins in hospitals is associated with good functional prognosis [629]. A retrospective study assessing compliance of patients after initiating statins for the treatment of ischemic stroke for 3 months indicated that these included patients maintained high medication compliance

and achieved somewhat good functional prognosis 3 months after discharge [630]. In a large cohort study with analysis of 12 years of studies, it was found that increased stroke recurrence would appear within 1 year in stroke patients who were prescribed lipid-lowering statins at the time of discharge if they stopped taking statins within 2-6 months after a stroke event [631].

Recommendations

ASCVD patients with ischemic stroke and other complications should be managed through lifestyle improvements, dietary advice, and drug treatment (Class I, Level of Evidence A).

(VII) Safety of application of high-intensity statins

High-intensity statins should be used with caution in the elderly, patients with impaired liver function, renal insufficiency or high-risk populations with adverse reactions that could potentially interact with combined drugs [632]. In consideration of the safety of statin therapy, comprehensive assessment on the types and doses of statins should be conducted in male, non-pregnant and non-lactating female based on patients' characteristics, risk of coronary atherosclerotic heart disease (calculated using data from multiple cohorts), and potential adverse reactions. For patients with multiple comorbidities, including renal insufficiency, liver insufficiency, previous statin intolerance or muscle disease, unexplainable elevation of alanine transaminase

more than three times the normal value, statin metabolism affected by the patient's own cause or drug combination, and patients over 75 years old, medium-intensity statins are preferred to high-intensity statins. Other factors influencing the selection of statin intensity include, but are not limited to, history of haemorrhagic stroke and the Asian population [612, 633-634]. In the above population, the application of statins in combination with ezetimibe is safe, which can achieve better lipid-lowering effects and effectively improve cardiovascular prognosis, especially in patients with a history of ischemic stroke [635-638].

Recommendations

[1] For ASCVD patients, it was originally intended to be treated with high-intensity statins. But when patients have contraindications or possible adverse reactions to statins, moderate intensity statins should be used as a second option. (Class I, Level of Evidence A).

[2] For clinical ASCVD patients over 75 years old, the benefits of reducing ASCVD risk, adverse drug reactions, drug-drug interactions and patient's wishes should be evaluated when initiating moderate or high-intensity statins. It is reasonable to continue statins in patients who can tolerate (Class IIb, Level of Evidence C).

See Figure 10 for the management process of lipid-lowering in patients with acute

ischemic stroke.

III. Management of abnormal glucose metabolism

Hyperglycaemia is common in patients with AIS. Multiple studies have shown that more than 40% of AIS patients show elevated blood glucose on admission, and most have a previous history of diabetes [639- 640]. Blood glucose elevation in stroke patients may be related to the non-fasting state, as well as impaired glucose metabolism under stress. Multiple observational studies have shown that blood glucose elevation at admission and in hospital is associated with poor clinical prognosis [641-642]. In patients receiving intravenous thrombolytic therapy, hyperglycaemia may be associated with symptomatic bleeding conversion and poor prognosis [100, 643-644]. In addition, multiple studies have indicated that AIS is associated with poor prognosis caused by massive cerebral infarction [645-647]. Although many observational studies have shown that elevated AIS blood glucose is associated with poor prognosis, it is uncertain whether there is a direct causal connection between the two.

It is generally accepted that hyperglycaemia should be controlled after stroke, but there are only a few randomized controlled trials on hypoglycaemic measures and target blood glucose values [499, 648-651], and no final conclusion has been reached. It is reasonable to control blood glucose at 140-180 mg/dl based on previous guidelines. The incidence of hypoglycaemia is low after stroke. Although there is no clinical trial on hyperglycaemic treatment, hypoglycaemia should be corrected as soon as possible

because it can directly cause cerebral ischemic injury and aggravated oedema, resulting in poor prognosis.

There are several large-scale RCT studies on intensified blood glucose management to reduce the risk of stroke and cardiovascular disease.

The ACCORD study [652] has evaluated whether intensive control of glycated haemoglobin to a normal target value can reduce cardiovascular disease events in type 2 diabetes patients with cardiovascular disease or cardiovascular risk factors. In this study, a total of 10,251 patients with average HbA1c of 8.1% were randomly divided into intensive treatment group using multiple drugs including insulin and oral hypoglycaemic drugs (target HbA1c value < 6.0%) or standard treatment group (target value: 7.0%-7.9%). As the death rate due to any cause was somewhat high in the intensive treatment group, it was stopped early (*HR*=1.22, 95% *CI:* 1.01-1.46, *P*=0.04). Although the average HbA1c value decreased from baseline 8.1% to 6.7% (intensive treatment group) and 7.5% (control group) at 4 months, the primary endpoint risk associated with intensive hypoglycaemic treatment (non-fatal MI, non-fatal stroke or cardiovascular death) didn't decrease (6.9% vs. 7.2%, *HR* = 0.90, 95% *CI:* 0.78-1.04, *P* = 0.16). Patients in the intensive treatment group required more frequent glucose-lowering drugs as adjuvant therapy (10.5% *vs.* 3.5%).

Another study evaluated the role of intensive glucose control in diabetic patients with poor control. After five to six years of follow-up, HbA1c values of patients in the intensive glycemic control group were significantly reduced, and no significant

differences in the primary and secondary endpoints were found between the two groups, including stroke risk (the number of events, 26 *vs.* 36, *HR*=0.78, *CI:* 0.48-1.28) or TIA (19 *vs.*13, *HR*=1.48, 95% *CI:* 0.73-2.99). The incidence of hypoglycaemic event increased significantly in the intensive treatment group [653].

In the ADVANCE study, 11,140 patients with type 2 diabetes were randomly divided into standard glucose-lowering group and intensive glucose-lowering group. The HbA1c value of the intensive glucose-lowering group was reduced to at least less than 6.5% by drugs. After 5 years of follow-up, it was found that the average HbA1c value of the intensive treatment group was lower than that of the standard group (6.5% *vs.* 7.3%) [654]. The incidence of major complications such as macrovascular and microvascular events in intensive treatment group was reduced (18.1% *vs.* 20.0%, *HR*=0.90, 95%*CI:* 0.77-0.97, *P*=0.01). There was no significant difference in mortality risk between the two groups (*HR*=0.93, 95% *CI* 0.83-1.06, *P*=0.28).

A meta-analysis covering the results of the above three studies evaluated the role of intensive glucose-lowering treatment in the prevention of vascular events in patients with type 2 diabetes, with an average follow-up of 5 years. The average HbA1c values were 6.6% (intensive group) and 7.4% (control group [655]. The incidences of all-cause death risk, stroke and cardiovascular mortality were not reduced in the intensive glucose-lowering treatment; however, the incidence of non-fatal myocardial infarction was significantly reduced by 14% (*RR*=0.86, 95% *CI:* 0.77-0.97, *P*=0.015).

Recommendations

[1] The prognosis of persistent hyperglycaemia in AIS patients within 24 hours after onset is worse than that of normal blood glucose. So, it is reasonable to control blood glucose to the range between 140~180mg/dL. At the same time, blood sugar should be closely monitored to prevent hypoglycaemia (Class IIa, Level of Evidence C).

[2] Treatment should be given to AIS patients with hypoglycaemia (blood glucose < 60mg/dL) (Class I, Level of Evidence C).

[3] It is recommended that ischemic stroke or TIA patients with diabetes should be evaluated and given the best management guideline (Class I, Level of Evidence A).

[4] For all inpatients/outpatients with ischemic stroke or TIA, rapid blood glucose, 2 hours postprandial blood glucose, glycosylated haemoglobin or 75g oral glucose tolerance test are recommended for screening diabetes mellitus (Class IIa, Level of Evidence C).

[5] Lifestyle and/or drug intervention in patients with diabetes or prediabetes can reduce ischemic stroke or TIA events. The recommended treatment target for glycosylated haemoglobin is ≤ 7% (Class I, Level of Evidence B).

[6] The hypoglycaemic regimen should consider the clinical characteristics of patients and the safety of drugs. To set up individual blood glucose control

targets, one should be vigilant against the harm caused by hypoglycaemic events (Class IIa, Level of Evidence B).

IV. Management of other risk factors

Many studies have shown that smoking is an independent risk factor for ischemic stroke [656-660].A multicentre prospective study on Chinese intracranial atherosclerosis (CICAS) shows that smoking is dose-related to the occurrence of extracranial atherosclerosis, but not related to intracranial atherosclerosis [661].

A large number of studies have found that Obstructive Sleep Apnoea is associated with stroke. Obstructive Sleep Apnoea is common in stroke patients and is associated with a high incidence of the following events, including cardiovascular and cerebrovascular events, poor prognosis and higher mortality. Continuous positive pressure ventilation is still the most effective method to treat apnoea. However, a RCT study shows that continuous positive pressure ventilation for patients with moderate to severe apnoea has no benefit in preventing cardiovascular events or deaths in patients with a history of stroke [662]. Therefore, routine screening of apnoea for secondary prevention of cardiovascular events or death is not helpful for all AIS patients.

The National Institute of Alcohol Abuse and Alcoholism defines heavy drinking for men as drinking more than 4 units per day or more than 14 units per week, and defines heavy drinking for women as drinking more than 3 units per day or more than

7 units per week. So far, the correlation between alcohol intake and stroke is still controversial. Many research results show that heavy drinking is a risk factor for various types of stroke [663-669].

In general, a large number of observational studies show that light to moderate drinking is associated with overall and ischemic stroke risk reduction, while heavy drinking increases the stroke risk. Many prospective randomized clinical trials show that heavy drinking can increase the risk of stroke but a small amount of drinking will reduce the risk of stroke, which lacks ethical support, because alcohol dependence is a major health problem.

Three large sample retrospective studies have found that hormone replacement therapy have no significant correlation with the occurrence, severity and prognosis of stroke [670-672]. Cheetham[673] found in a retrospective cohort study with a sample size of 8808 that men receiving androgen replacement therapy had a lower incidence of cardiovascular events than men who had never received such therapy. Sidney found in a retrospective cohort study that the incidence of thromboembolism events in oral contraceptives was higher than that in non-oral contraceptives [674].

In recent years, the research on the relationship between oral contraceptives/hormone replacement therapy and stroke has shown a significant growth trend in China. Specifically, four retrospective cohort studies have [675-678] found that oral contraceptives are related to the increased risk of cerebral haemorrhage, especially when patients have a history of hypertension.

Some studies have proved that there is a causal relationship between acute narcotic drug use and the risk of early ischemic stroke, rather than previous use of narcotic drugs [679]. In addition, studies have shown that people with stroke related to narcotic drug abuse are younger, tend to have a smoking history, and have less traditional risk factors such as hypertension, diabetes, and hyperlipidaemia [680-682].

Two large-sample meta-analyses based on population cohort studies found that reducing homocysteine by 25% can reduce stroke risk by 11%-16% [683-684].However, clinical trials of folic acid supplementation for secondary prevention of CVD or stroke have not found that supplementation of homocysteine-reducing vitamins can reduce the risk of recurrent stroke. Currently, there is a lack of large-sample studies of homocysteine-related genes (*MTHFR* 677C- > T) and stroke risk [685].The Vitamin Intervention for Stroke Prevention (VISP) study randomly divided the non-cardiac stroke patients into groups, and the patients with mild to moderate hyperhomocysteinemia received high-dose or low-dose vitamin therapy for 2 years. The results showed that the risk of stroke was related to the homocysteine level, the average reduction of the homocysteine level in the high dose vitamin treatment group was larger, but the risk of stroke did not decrease [686]. The "Vitamins to Prevent Stroke" trial (VITATOPS) also failed to prove that vitamin therapy can prevent stroke, myocardial infarction or vascular death in patients with recent stroke or TIA [687].

Recommendations

[1] Healthcare staff should strongly recommend that all AIS patients who have smoked in the past year quit smoking (Class I, Level of Evidence C).

[2] For AIS patients who smokes, consider to starting intervention measures combined with drug therapy and behavioural support during hospitalization (Class IIb, Level of Evidence B).

[3] Routine screening for obstructive sleep apnoea in patients with recent ischemic stroke is not recommended (Class III, Level of Evidence B).

[4] For alcohol drinkers, it may be reasonable for men to drink ≤ 2 units and non-pregnant women to drink ≤ 1 unit per day (Class IIb, Level of Evidence B).

[5] The relationship between oral contraceptives and stroke needs to be further confirmed in prospective studies. Oral contraceptives may be associated with haemorrhagic stroke, which is more pronounced in patients with hypertension. So oral contraceptive is not recommended for patients with hypertension (Class III, Level of Evidence C).

[6] The relationship between drug use and stroke needs to be further studied. Acute drug use may be a risk factor for stroke and a factor for poor prognosis (Class III, Level of Evidence C).

[7] For patients with recent ischemic stroke or TIA and mild to moderate increase in blood homocysteine, Folic acid, vitamin B6 and vitamin B12 supplementation can reduce the level of homocysteine. There is not enough evidence to support the practice of reducing homocysteine levels to reduce the

risk of stroke recurrence (Class IIb, Level of Evidence B).

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Supplemental Table 1 Flow chart of skull imagological examination for patients suspected of ischemic stroke after entering emergency department

All patients suspected of acute stroke		
Time point	Imaging examination	Main assessment content
Within 30min after entry into emergency department	NCCT	Exclusion of haemorrhage ASPECTS ≥ 6 indicates macrovascular occlusion
Indications for intravascular treatment for suspected macrovascular occlusion		
Time point	Imaging examination	Main assessment content
Within 6h of onset	CTA	Whether there is macrovascular occlusion
Within 16h after onset	DWI/PWI or CTP	Whether compliance with DAWN or DEFUSE3 standard
Within 24h after onset	DWI/PWI or CTP	Whether compliance with DAWN standard

Supplemental Table 2 Set thresholds of different imaging strategies for ischemic penumbra

Imaging strategy	Set threshold for ischemic penumbra
DWI-PWI mismatch	The area with T_{max} > 6s on PWI is set as the low perfusion area, the area with ADC < $600\times10^{-6}mm^2/s$ on DWI is set as the infarction core area, the target mismatch is defined as infarction core area < 70ml, ischemic penumbra > 15ml, and the ratio of total low perfusion area to ischemic core area of > 1.8
CT PWI	The area with CBF lower than 30% of the normal tissue on the affected side is set as the infarction core lesion, the area with T_{max} > 6s is set as the low perfusion area, and the definition of target mismatch is the same as before.
Clinical imaging mismatch	The patients were divided into three groups according to the size, age and NIHSS score of the imaging lesion: Group A was over 80 years old, NIHSS score ≥ 10 and infarction core < 21ml. Group B was under 80 years old, NIHSS score ≥ 10 and infarction core < 31ml. Group C was under 80 years old, NIHSS score ≥ 20 and infarction core of 31--51ml.
DWI-FLAIR mismatch	Lesions can be seen on DWI but there is no high signal on the corresponding parts of FLAIR

Supplemental Table 3 Indications and contraindications of rt-PA intravenous thrombolysis within 3h

Indications
1. There are neurological impairment symptoms caused by ischemic stroke
2. Occurrence of symptoms < 3h
3. Age ≥ 18 years
4. Patients or their families sign the informed consent form
Contraindications
1. Intracranial hemorrhage (such as cerebral parenchyma hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, subdural / epidural hematoma)
2. History of intracranial haemorrhage
3. Severe head trauma or stroke in the past 3 months
4. Intracranial tumour, giant intracranial aneurysms
5. Recent (in 3 months) intracranial or intraspinal surgery
6. Major surgeries in the last two weeks
7. Gastrointestinal or urinary system bleeding in the last 3 weeks
8. Active internal haemorrhage
9. Aortic arch dissection
10. Arterial puncture in a site where haemostasis by compression is not easy to within the past week
11. Elevation of blood pressure, systolic pressure ≥ 180mmHg or diastolic pressure ≥

100mmHg

12. Acute haemorrhagic tendency, including platelet count below 100× 109/L or other conditions
13. Receipt of low molecular weight heparin treatment within 24h
14. INR > 1.7 or PT > 15s for patients who have taken anticoagulant orally
15. Thrombin inhibitors or Xa factor inhibitors are being used within 48h, or the results of laboratory tests are abnormal (such as APTT, INR, platelet count, ECT; TT or appropriate Xa factor activity determination)
16. Blood glucose < 2.8mmol/L or > 22.22 mmol/L
17. Head CT or MRI indicates a large area of infarction (infarct size > 1/3 the blood supply area of middle cerebral artery)

Relative contraindications

The risks and benefits of thrombolysis should be carefully considered and weighed in the following situations (i.e. although there are one or more relative contraindications, thrombolysis is not absolutely impossible):

1. Minor non-disabling stroke
2. Stroke with rapid improvement of symptoms
3. Neurological impairment symptoms after epileptic seizure (associated with this stroke)
4. Extracranial cervical arterial dissection
5. Severe trauma in the past 2 weeks (no head injury)
6. History of myocardial infarction in the past 3 months

7. Pregnancy
8. Dementia
9. Severe neurological disability left by previous diseases
10. Unruptured and untreated arteriovenous malformations and small intracranial aneurysms (< 10mm)
11. A small amount of intracerebral microhemorrhage (1~10)
12. Use of prohibited drugs
13. Stroke mimics

Supplemental Table 4 Indications and contraindications of rt-PA intravenous thrombolysis within 3--4.5h

Indications
1. There are neurological impairment symptoms caused by ischemic stroke 2. Symptom occurrence 3-4.5h 3. Age ≥ 18 years 4. Patients or their families sign the informed consent form
Contraindications
Same as Supplemental Table 3contraindications
Relative contraindications
The risks and benefits of thrombolysis should be carefully considered and weighed in the following situations (i.e. although there are one or more relative contraindications, thrombolysis is not absolutely impossible): 1~13 items are the same as those in Supplemental Table 3 Relative contraindications. 14. INR ⩽ 1.7 and PT ⩽ 15s for patients who have taken anticoagulant orally 15. Severe stroke (NIHSS score > 25)

Supplemental Table 5 Blood pressure control for thrombolysis

Other than patients with blood pressure > 185/110mmHg, for patients suitable for acute reperfusion therapy:

Labetalol 10--20 mg is injected intravenously for 1--2 min, which may be repeated once;

Nicardipine 5mg/h intravenous injection. After every 5--15 min, the dripping speed can be increased by 2.5mg/h, and the maximum dripping speed is 15 mg/h. When the expected blood pressure value is reached, the dripping speed should be adjusted to maintain the ideal blood pressure;

Clovidipine is injected intravenously at 1--2 mg/h. The dripping speed can be doubled every 2--5 minutes until the expected blood pressure is reached, with the maximum dripping speed being 21 mg/h;

Other drugs, such as hydralazine and enalapril, may also be considered.

Thrombolytic therapy must not be performed if the blood pressure is not maintained at ≤ 180/110mmHg.

In the blood pressure management during thrombolysis, after thrombolysis or other acute reperfusion therapy, the blood pressure should be maintained at ≤ 180/105mmHg.

Blood pressure should be monitored every 15min in 2h, every 30min in 6h, and once every hour in 16h after thrombolytic therapy.

If SBP > 180--230mmHg or DBP > 105--120mmHg:

Labetalol 10mg intravenous injection is followed by intravenous infusion of 2--8 mg/min;

Nicardipine 5mg/h intravenous injection. After every 5--15 min, the dripping speed can be

increased by 2.5mg/h to reach the expected blood pressure value. The maximum dropping speed is 15 mg/h;

Clovidipine is injected intravenously at 1- 2 mg/h. The dripping speed can be doubled every 2- 5 minutes until the expected blood pressure is reached, with the maximum dripping speed being 21 mg/h;

If blood pressure is not controlled or diastolic pressure is > 140mmHg, intravenous injection of sodium nitroprusside should be considered.

Supplemental Table 6 Monitoring and handling of intravenous thrombolysis

1.Patients should be admitted to a neurological intensive care unit or a stroke unit for monitoring
2. Regular blood pressure and neurological function tests should be carried out. Blood pressure measurements and neurological function assessments should be carried out every 15min within 2 hours after intravenous thrombolytic therapy is completed. After that, they should be carried out every 30min for 6 hours, then once every hour until 24 hours after the end of treatment
3. In case of severe headache, hypertension, nausea or vomiting, or deterioration of neurological symptoms and signs, thrombolytic drugs should be withdrawn immediately and head CT examination should be performed
4.In case of SBP ≥ 180mmHg or DBP ≥ 105mmHg, the frequency of blood pressure monitoring should be increased and antihypertensive drugs should be given
5.Placement of nasal feeding tube, urethral catheter and intra-arterial pressure tube should be delayed when the condition permits
6.24h after thrombolytic therapy, head CT or MRI should be performed again before antiplatelet drugs or anticoagulants are given

Supplemental Table 7 Imaging screening criteria beyond time windows in different studies

Study name	Inclusion criteria
DAWN study	① The time from the last seemingly normal time of the patient to randomization was 6--24 h. ② The screening scheme is that the severity of clinical neurological impairment symptoms does not match the infarct volume-"clinical-imaging mismatch" (NIHSS score does not match the infarct volume of MRI-DWI/CTP-rCBF), which is defined as: Group A: ≥ 80 years, NIHSS score ≥ 10, infarct volume < 21ml Group B: < 80 years, NIHSS score ≥ 10, infarct volume < 31ml Group C: < 80 years, NIHSS score ≥ 20, infarct volume < 51ml
DEFUSE 3 study	Preoperative mRS score ≤ 2, aged 18-90 years The time from onset to start of intravascular treatment is 6-16h DWI or CTP cerebral infarction core volume ≤ 70ml Ratio of hypoperfusion area/infarction area volume ≥ 1.8 or mismatch volume between hypoperfusion area and infarction area > 15ml

Refer to Figure 3 for details of the treatment process of intravascular treatment for patients with acute ischemic stroke.

Supplemental Table 8 Antiplatelet drugs commonly used for ischemic stroke

Medication plan	Target and mechanism of action	Indication
Aspirin	Through irreversible acetylation with hydroxyl group of serine residue 530 in polypeptide chain of COX-1 active site in cyclooxygenase (COX), Cox is inactivated, thus blocking the pathway of AA conversion to thromboxane A2 (TXA2) and inhibiting platelet aggregation	AIS patients should take it within 24-48h after onset. For patients treated with intravenous alteplase, aspirin is usually postponed until 24h later (however, in the case of some complications, in the absence of intravenous alteplase treatment, if it is known that administration of aspirin can bring significant benefits or the absence of aspirin will cause significant risks, not postponing it may be considered) Aspirin as substitute for treatment is not recommended for acute stroke patients who are suitable for intravenous thrombolysis with alteplase or mechanical thrombectomy

Clopidogrel	It selectively inhibits ADP binding to platelet receptors and inhibits ADP-mediated activation of glycoprotein (GP)IIb/IIIa complex, thus inhibiting platelet aggregation. It can also inhibit platelet aggregation not caused by ADP. Its effect on platelet ADP receptor is irreversible. Its oral absorption is rapid, the protein binding rate in plasma is 98%, and it is metabolized in liver	For patients with mild stroke and TIA of medium and high risk, dual antiplatelet therapy (aspirin 100mg/ time, qd, combined with clopidogrel 75mg/ time, qd, clopidogrel loading dose 300mg on the first day) should be started within 24 hours of onset, which is beneficial to prevent early stroke recurrence within 90 days of onset For mild stroke patients complicated with high-risk intracranial arterial stenosis (70%-99%), combined stent therapy is not recommended on the basis of dual antiplatelet therapy (aspirin combined with clopidogrel)
Ticagrelor	It is a selective ADP receptor antagonist that acts on P2Y12 ADP receptor to inhibit ADP-mediated platelet activation and aggregation, with similar mechanism of action of thienopyridine drugs (such as clopidogrel). However, the	Ticagrelor (instead of aspirin) is not recommended for acute treatment of mild stroke

	difference is that the interaction between ticagrelor and platelet P2Y12 ADP receptor is reversible, with no conformational change and signal transmission, and the platelet function in blood also recovers rapidly after drug withdrawal	
Cilostazol	By inhibiting phosphodiesterase activity in platelets and vascular smooth muscle, the cAMP concentration in platelets and smooth muscle is increased to give play to the antiplatelet effect and vasodilation effect. It inhibits platelet aggregation and release reactions induced by ADP, epinephrine, collagen and arachidonic acid, and has obvious antithrombotic effect on models of cerebral circulation and peripheral circulation disorders induced by collagen, ADP, arachidonic acid and	Cilostazol can be used in AIS patients and as an alternative to aspirin

	sodium laurate	
Indobufen	It reversibly inhibits COX-1, inhibits platelet aggregation induced by ADP, epinephrine, collagen and arachidonic acid, and exerts antiplatelet effect. In addition, it can also reduce platelet factor 3 and platelet factor 4, significantly inhibit coagulation factor II and coagulation factor X, and has anticoagulant effect	For patients with aspirin intolerance (with gastrointestinal reaction or allergy, etc.) and a high risk of haemorrhage, it is feasible to use indobufen (100mg/ time, bid)
Dipyridamole	It inhibits platelet uptake of adenosine, inhibits phosphodiesterase and increases platelet cAMP, and is a atrong agonist that inhibits TXA2 formation and TXA2 platelet activity, and enhances endogenous prostacyclin (PGI2)	Whether dipyridamole antithrombotic monotherapy is more beneficial to secondary prevention of cerebral infarction still needs to be confirmed by a large number of RCTs
Abciximab	Namely the "anti-platelet aggregation monoclonal antibody",	It may be harmful to AIS treatment

	which can selectively block platelet glycoprotein IIb/IIIa receptor and prevent fibrinogen, platelet-activating factor (PAF), vitreous binding protein and fibrin binding protein from binding to activated platelets	
Tirofiban	It is a reversible non-peptide platelet surface GPIIb/IIIa receptor antagonist. It competitively inhibits the binding of fibrinogen to platelet GPIIb/IIIa receptor, inhibits platelet aggregation, prolongs bleeding time, and inhibits thrombosis	The efficacy and safety have not yet been determined and need further confirmation
Eptifibatide	It selectively blocks the binding of adhesion protein to GPIIb/IIIa, and is also a relatively weak inhibitor of most related receptors	The efficacy and safety have not yet been determined and need further confirmation

Supplemental Table 9 Type of haemorrhagic transformation in ischemic stroke

Type	Definition	Scanning time point
Asymptomatic intracranial haemorrhage	Imaging examination shows intracranial haemorrhage, but there is no neurological deterioration in the patient	
Symptomatic intracranial haemorrhage		
NINDS	CT finds haemorrhage + any neurological function decline	24 hours after onset, 7-10 days after onset or when clinical symptoms suggest haemorrhage
ECASS II	Any haemorrhage + NIHSS score increase ≥ 4 points	22-36h and 7d after treatment or when clinical symptoms aggravate
SITS-MOST	Hematoma volume at infarction site or distant site > 30% of infarction volume, with obvious mass effect + NIHSS score increase ≥ 4 points	22-36h after treatment
ECASS III	Any haemorrhage + NIHSS score increase ≥ 4 points, and it is determined that	22-36h after CT or MRI treatment

haemorrhage is the main cause of

neurological deterioration

Supplemental Table 10 Essen stroke risk score

Risk factors	Score/points	Risk factors	Score/points
Aged 65~75 years	1	Other cardiovascular diseases (except for myocardial infarction and atrial fibrillation)	1
Age > 75 years	2		
Hypertension	1	Peripheral arterial disease	1
Diabetes	1	Smoking	1
History of myocardial infarction	1	History of TIA or ischemic stroke	1
Total score		9	

Supplemental Table 11 CHADS2 score and CHA2DS2-VASc score

CHADS2 risk factors	Score/points	CHA2 DS2-VAScrisk factors	Score/points
Heart failure	1	Heart failure	1
Hypertension	1	Hypertension	1
Age > 75 years	1	Age > 75 years	2
Diabetes	1	Diabetes	1
History of stroke/TIA	2	History of stroke/TIA	2
		Peripheral vascular disease	1
		Aged 65~74 years	1
		Female	1

Supplemental Table 12 Stratified assessment of stroke risk for atrial fibrillation patients

CHADS2	Low risk	Intermediate risk	High risk
Classic CHADS2 score	0	1~2	3~6
Modified CHADS2 score	0	1	2~6
CHA2DS2-VASc score	0	1	2~9

Supplemental Table 13 HAS-BLED scale

Risk factors	Score	Risk factors	Score
Hypertension	1	Labile INR	1
Abnormal liver and/or kidney function	1/2 (1 point for liver and 1 point for kidney)	Elderly (age > 65 years)	1
History of stroke	1	Drugs and/or alcohol	1/2 (1 point for drugs and 1 point for alcohol)
History or tendency of haemorrhage	1		

Supplemental Table 14 SPI-II scale

Item	Score/points	Item	Score/points
Age > 70 years	2	Coronary atherosclerotic heart disease	1
SBP > 180mmHg or DBP > 100mmHg	1	History of stroke	3
Diabetes	3	Congestive cardiac failure	3
Stroke events (non-transient ischemic attack)	2		

Supplemental Table 15 Comparison table of doses of lipid-lowering drugs

Low intensity lipid-lowering treatment Lower LDL-C < 30%	**Moderate intensity lipid-lowering treatment Lower LDL-C 30%-49%**	**High intensity lipid-lowering treatment Lower LDL-C 50%-60%**	**Ultra-high intensity lipid-lowering treatment Lower LDL-C > 60%**
Simvastatin 10mg	Atorvastatin 10-20mg	Atorvastatin 40-80mg	Atorvastatin 40-80mg + Ezetimibe 10mg
Vastatin 10-20mg	Rosuvastatin 5-10mg	Rosuvastatin 20-40mg	Rosuvastatin 20-40mg + ezetimibe 10mg
Lovastatin 10-20mg	Simvastatin 20-40mg	Simvastatin 20-40mg + Ezetimibe 10mg	
Fluvastatin 40mg	Pravastatin 40mg	Pravastatin 40mg + Ezetimibe 10mg	
Pitavastatin 1mg	Lovastatin 40mg	Lovastatin 40mg + Ezetimibe 10mg	
Ezetimibe 10mg	Fluvastatin XL 80mg	Fluvastatin 80mg + Ezetimibe 10mg	

Pitavastatin 2-4mg	Pitavastatin 2-4mg + Ezetimibe 10mg
Simvastatin 10mg + Ezetimibe 10mg	Atorvastatin 10-20mg + Ezetimibe 10mg
Pravastatin 20mg + Ezetimibe 10mg	Rosuvastatin 5-10mg + Ezetimibe 10mg
Lovastatin 20mg + Ezetimibe 10mg	
Fluvastatin 40mg + Ezetimibe 10mg	
Pitavastatin 1mg + Ezetimibe 10mg	