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## Part 1: CDSS system

### 1. Obtaining Clinical Information

The CDSS is deployed in the medical intranet environment of each hospital with a C/S architecture. The server and client are provided by the project team, and the network environment requires a network bandwidth of 100 Mbps and a local area network. The input data of the system come from the hospital information system (HIS), laboratory information management system (LIS), electronic medical record (EMR), and picture archiving and communication system (PACS) of the user institution, including the patient's clinical information and imaging data. (Figure s1).

The methods of data collection by the system are as follows: (1) The data views of the HIS database and the LIS database are read through the JDBC protocol to obtain patient clinical data, and incremental data are obtained regularly; (2) The PACS service is connected through the DICOM protocol to acquire image data. The data integrity and quality affect the accuracy of clinical decision-making recommendations. All clinical data were confirmed by the doctor before entering the analysis. To ensure the accuracy of the extracted information, the manual mode is also available, allowing physicians to check and confirm the accuracy of important information that is automatically extracted and revise it when necessary. For the unstructured EMR data, the system cannot automatically capture, the missing data are marked with a red box on the client page, and the doctor needs to manually input those data necessary for the system to assist in decision-making. Missing DWI b1000 sequences will lead to failure of AI image analysis, and poor image quality will affect the accuracy of image analysis results. The system will set the infarction mode to a modifiable mode and ensure that all centers receive training on image acquisition practices before the study begins.

The collected data are as follows: a) Basic demographic information: age, sex, disease history, medication history, and risk factors for vascular disease. b) Clinical characteristics: clinical symptoms, blood pressure, and results of physical examination.

c) Results of laboratory tests: blood lipids, blood sugar, HbA1c, liver and kidney function, coagulation function. d) Imaging examination of head structure: head CT, brain MRI. e) Evaluation of vascular function: intracranial and extracranial vascular examination (head and neck vascular ultrasound/TCD/MRA/CTA), aortic arch examination, examination of peripheral vascular function. f) Cardiac examination: ECG, ECG Holter monitoring >24 hours, transthoracic/transesophageal echocardiography, TCD foaming test. g) Rating scales: NIH Stroke Scale Score (NIHSS).

## **2. AI-assisted Imaging Analysis**

A deep learning algorithm was developed for automatic segmentation of ischemic lesions based on DWI and ADC scans using a large national data set from the Third China National Stroke Registry (CNSR-III) study. It reached an overall median Dice score of 0.910 (0.839–0.935), indicating a good lesion identification performance.

Depending on the deep learning algorithm, the CDSS provides information on infarct characteristics, including infarct number, infarct diameter/volume, infarct anatomy, and responsible blood supplies. (Figure s2)

## **3. The etiology and pathogenesis of ischemic stroke**

The CDSS automatically reads the preset clinical information related to etiological classification, integrates the information from the electronic medical records and imaging, and analyzes the etiology and pathogenesis of ischemic stroke according to the Trial of Org10172 in Acute Stroke Treatment (TOAST) and the Chinese Ischemic Stroke Subclassification (CISS) (Figure s3). For patients with incomplete examinations of which the etiology cannot be determined, the system provides the list of examinations that need to be completed to clarify its etiology.

## **4. Guideline-based treatment recommendations**

Based on the clinical guidelines of cerebrovascular disease in China and referring to Chinese and foreign authoritative guidelines and evidence-based medical evidence,

the decision process and knowledge base for the diagnosis and treatment of ischemic stroke are constructed. All of the medical logic and medical content was verified by authoritative medical experts. The treatment strategy is provided by matching the clinical characteristics and stroke etiology of participants with the evidence-based guidelines, including strategies for the acute phase and secondary prevention, that is antithrombotic therapy, blood lipid management, blood pressure management, blood sugar management, and other recommendations. The CDSS will also provide information from the guidelines and RCTs (Supplementary Material Part 2). Clinicians can choose to follow or not follow those recommendations and then record their own decision (this record will be confirmed by checking the prescription from the clinician).

## **5. Evaluation and Feedback of Medical Care Quality of Stroke**

The hospital in the intervention group systematically evaluates and summarizes the implementation of the preset medical care service for acute ischemic stroke using the CDSS (Table s1), and feedback is provided every 2 weeks. The quality improvement committee is responsible for supervising adherence to stroke care quality standards. Regular CDSS training sessions are also conducted to ensure that clinicians can use the system correctly and effectively.

## **6. Application process**

Specifically, on the day of admission, the system suggests a preliminary diagnosis and treatment recommendations according to patient information. At the same time, the CDSS will advise clinicians of further improved examinations. After the relevant examinations are completed, including the MRI image, the CDSS automatically performs image analysis based on deep learning technology, outputs infarct pattern and infarct characteristic parameters. Based on clinical information and imaging features, classification of the etiology and pathogenesis of ischemic stroke is performed to provide guideline-based treatment recommendations for acute and secondary prevention. In addition, the CDSS will undergo continuous quality control through the medical quality index evaluation and feedback process on this process.

The physicians’ acceptance of the infarction patterns, etiological classification and treatment recommendations output by the software will be collected through CDSS. Device failures (e.g., system failure to start, failure to obtain patient data, failure to input data or output decision recommendations, system crash, etc.), and adverse medical events or worsening of preexisting medical events in subjects during the use of CDSS, despite a potential causal relationship with CDSS, will be recorded by the investigator.

**Table s1. Preset indicators of stroke medical care service**

ID	Indicators	Definition
<b>Indicators during the acute phase</b>		
1	Aspirin or other antithrombotic medication within 48 hours of admission	Therapy using aspirin or other antithrombotic drugs for acute ischemic stroke within 48 hours of admission
2	Dual antiplatelet therapy in patients with nondisabling ischemic cerebrovascular disease within 24 hours of disease onset	Dual antiplatelet therapy with aspirin and clopidogrel within 24 hours of onset of nondisabling ischemic cerebrovascular disease (NIHSS $\leq$ 3 points)
3	Intensive statin therapy in noncardiac stroke patients	Intensive statin therapy during hospitalization in noncardiac stroke patients
4	Anticoagulation in patients with atrial fibrillation	Anticoagulant therapy in patients with acute ischemic stroke and atrial fibrillation during hospitalization
5	Hypoglycemic drug treatment in patients with diabetes	Administration of hypoglycemic drugs during hospitalization in patients with acute ischemic stroke complicated with diabetes mellitus

6	Antihypertensive treatment in patients with hypertension	Administration of antihypertensive drugs during hospitalization in patients with acute ischemic stroke and hypertension
7	Evaluation of swallowing function	Swallowing function evaluation in patients with acute ischemic stroke before eating or drinking via mouth.
8	Deep vein thrombosis prophylaxis	Patients with acute ischemic stroke who could not walk on their own were given prophylaxis for lower extremity deep vein thrombosis within 2 days of hospitalization.
<b>Indicators after discharge</b>		
1	Aspirin or other antithrombotic medication at discharge	aspirin or other antithrombotic drugs are provided to patients with acute ischemic stroke at discharge
2	Anticoagulation in patients with atrial fibrillation at discharge	Anticoagulant therapy in patients with acute ischemic stroke and atrial fibrillation at discharge
3	Antihypertensive treatment for patients with hypertension at discharge	Antihypertensive drugs administered to patients with acute ischemic stroke and hypertension at discharge
4	Statin therapy at discharge	Statin drugs are provided to patients with acute ischemic stroke at discharge
5	Use of hypoglycemic drugs in patients with diabetes at discharge	Hypoglycemic drugs are administered in patients with acute ischemic stroke complicated with diabetes mellitus at discharge

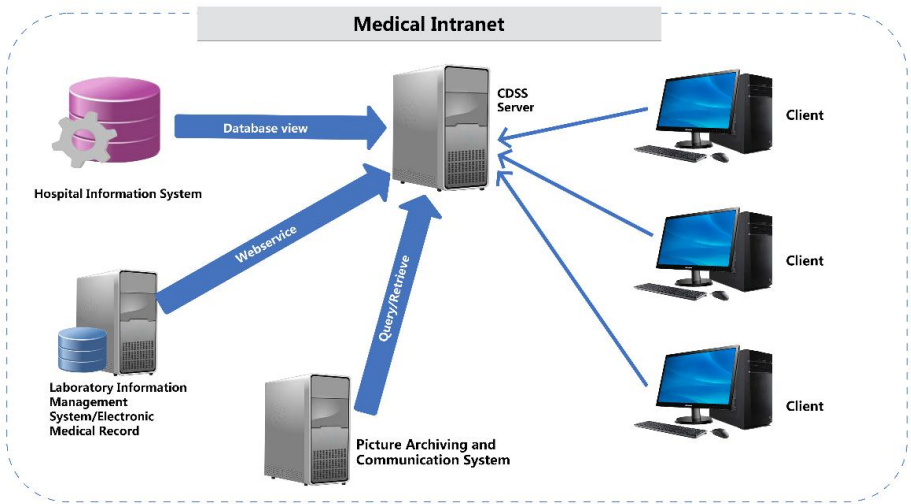


Figure s1. Network topology diagram of cerebrovascular disease CDSS.

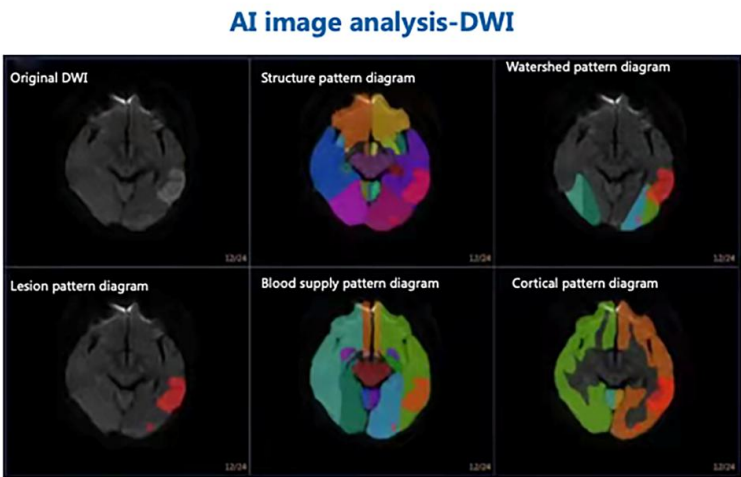


Figure s2. AI-assisted infarct imaging analysis.

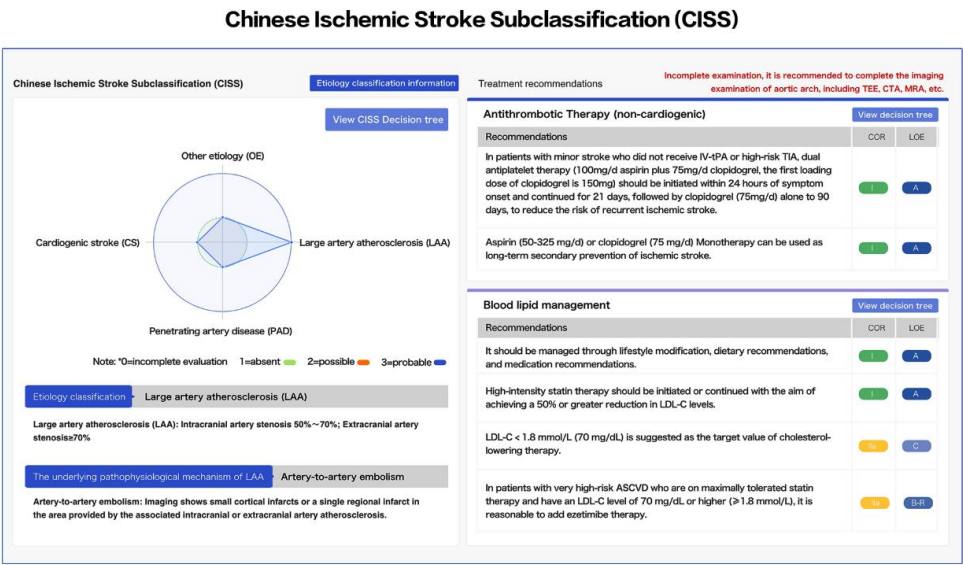


Figure s3. Analysis results of the ischemic stroke etiology and pathogenesis.



## Part 2: In-hospital management process of acute ischemic stroke

Stroke is the leading cause of death and disability in Chinese residents and is characterized by high morbidity, disability, and mortality. The burden of stroke in China is still increasing. China has the highest prevalence of stroke in the world, and the highest age-standardized incidence of stroke (354/100,000 per year). Ischemic stroke is the most common type of stroke and accounts for 60% to 80% of strokes in China.[1, 2] The early stage of acute ischemic stroke (AIS) is the peak period of stroke recurrence. [3] Improving in-hospital management of patients with AIS is conducive to reducing stroke recurrence and improving patient prognosis.

This study mainly presents the optimization of the in-hospital management process in patients with AIS in China, based on the *Guidelines for Clinical Management of Cerebrovascular Disorders in China* issued by Chinese Stroke Association and in combination with the recent international guidelines. In this article, we mainly introduce in-hospital antithrombotic therapy, blood lipid management, blood pressure management, blood glucose management, complication management, etiology and pathogenesis diagnosis of AIS and an efficient management flow for evidence-based recommendations for stroke treatment in clinical practice.

### 1 Antithrombotic Therapy

#### 1.1 Antithrombotic Therapy for Noncardiogenic Stroke

Aspirin is recommended in patients with AIS within 24-48 hours after onset. For patients treated with an intravenous tissue plasminogen activator (IV-tPA), aspirin administration is generally delayed until 24 hours later.

For patients receiving endovascular therapy, antiplatelet therapy should be routinely administered after mechanical thrombectomy in nonbridging patients. If emergency stent implantation is performed, a loading dose of 300 mg aspirin and 300 mg clopidogrel should be administered before the operation; then, 100 mg/d aspirin plus 75 mg/d clopidogrel for at least 1 month is recommended. In bridging patients, the risk of antithrombotic therapy within

24 hours after IV-tPA remains unclear. For patients receiving bridging therapy combined with emergency stent implantation, the safety of antithrombotic therapy to prevent acute stent thrombosis within 24 hours after intravenous thrombolysis is unclear.

In patients with minor noncardioembolic ischemic stroke (NIHSS score  $\leq 3$ ) who did not receive IV-tPA or had high-risk transient ischemic attacks (TIA) (ABCD<sup>2</sup> score  $\geq 4$ ), dual antiplatelet therapy (aspirin plus clopidogrel) was initiated within 24 hours of symptom onset and continued for 21 days, followed by clopidogrel alone for 90 days to reduce the risk of recurrent ischemic stroke. Among patients with minor ischemic stroke or high-risk TIA, who were also carriers of CYP2C19 loss-of-function alleles, an alternative treatment regimen of ticagrelor (180 mg on Day 1 followed by 90 mg twice daily on Days 2 through 90) combined with aspirin (for 21 days) should be used. Contraindications, especially the risk of bleeding, should be considered when using dual antiplatelet therapy.

In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, dual antiplatelet therapy (aspirin plus clopidogrel) should be used up to 90 days while monitoring the risk of bleeding.

Monotherapy antiplatelet therapy (aspirin or clopidogrel) can be used for the long-term secondary prevention of ischemic stroke.

The decision process for in-hospital antithrombotic therapy in patients with noncardiogenic stroke is shown in Figure 1A. The development of an in-hospital antithrombotic therapy process for patients with noncardiogenic stroke is mainly based on evidence of the following randomized controlled trial (RCT): CAST, IST, MATCH, CARESS, ESPRIT, CAPRIE, CLAIR, SAMMPRIS, CHANCE, POINT, THALAS, CHANCE-2, etc. (Table 1).[4-26]

## 1.2 Antithrombotic Therapy for Cardioembolism

### 1.2.1 Atrial fibrillation (AF)

AF is the most common cause of cardioembolic stroke. Recommendations based on the *2019 Chinese guideline for the prevention and treatment of cardiogenic stroke, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease* and *2021*

*Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack*

recommend the use of oral anticoagulants (e.g., apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) to reduce the risk of recurrent stroke in patients with nonvalvular AF, stroke or TIA. The target international normalized ratio (INR) for warfarin should be 2.0 to 3.0. Novel oral anticoagulants (NOACs) have a shorter half-life and causes less food-drug interactions than warfarin. NOACs do not require routine monitoring of coagulation, but they should be carefully administered in patients with severe renal dysfunction (creatinine clearance <30 mL/min). Renal function and hepatic function should be evaluated before NOACs are administered and reevaluated annually. It may be reasonable to administer warfarin or apixaban (dose adjusted if indicated) for anticoagulation and to reduce the risk of recurrent stroke in patients with AF, stroke or TIA who have end-stage renal disease or are receiving dialysis. It may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce the risk of recurrent stroke and bleeding in stroke or TIA patients with nonvalvular AF who have contraindications for lifelong anticoagulation but can tolerate at least 45 days of anticoagulant therapy. The timing of the initiation of anticoagulants still lacks adequate evidence. For most stroke patients with AF and a low risk of hemorrhagic transformation, it is reasonable to initiate anticoagulant therapy within 2-14 days after stroke onset to reduce the risk of stroke recurrence. For patients with a high risk of bleeding, the anticoagulation time should be appropriately prolonged. It is suggested that anticoagulation therapy can be initiated on Day 1 after TIA onset; anticoagulants should be initiated after 3 days in patients with mild stroke (< 1.5 cm; NIHSS < 8), after 6 days in moderate stroke patients (NIHSS 8-15) and after at least 12 days in severe stroke patients (NIHSS > 16).

**1.2.2 Valvular Disease**

In patients with ischemic stroke or TIA and valvular AF (moderate to severe mitral stenosis or any mechanical heart valve), warfarin is recommended with an INR target of 2.0-3.0 to reduce the risk of recurrent stroke or TIA.

All patients with mechanical valves should receive life-long anticoagulant therapy with warfarin and receive regular monitoring. In patients with mechanical mitral valve replacement,

anticoagulation with warfarin is recommended with an INR target of 2.0-3.0. In patients with mechanical aortic valve replacement, anticoagulation with warfarin is recommended to achieve an INR of 2.5–3.5. In patients with other high-risk factors (such as AF, previous stroke history, left ventricular dysfunction, hypercoagulable state), anticoagulation with warfarin is recommended, with an INR target of 2.0-3.0. In patients with mechanical valves, low-dose aspirin (75–100 mg/d) and warfarin are recommended and INR should be monitored to further reduce the risk of thrombosis.

In the first 3 months after mitral or tricuspid biological valve implantation, anticoagulation with warfarin (INR 2.0-3.0) is recommended for patients without other anticoagulant indications (such as AF). In the first 3-6 months after transcatheter aortic valve implantation, aspirin (75-100 mg/d) plus clopidogrel (75 mg/d) is recommended for antithrombotic therapy, and aspirin alone is recommended for long-term use. In the first 3 months after aortic biological valve implantation, anticoagulation with warfarin (INR=2.5) is recommended for patients without other anticoagulant indications (such as AF). For patients with rheumatic mitral stenosis without AF, warfarin (INR 2.0-3.0) or heparin anticoagulant therapy is recommended if the patient has a history of previous embolism or atrial thrombosis (including auricular). In ischemic stroke or TIA patients with nonrheumatic mitral valve disease or other valve diseases, such as local aortic arch, mitral annular calcification or mitral valve prolapse, without AF, antiplatelet therapy can be considered.

For patients with ischemic stroke or TIA complicated with infective endocarditis (IE) who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy, in the absence of intracranial hemorrhage and severe neurological damage, early surgery (during initial hospitalization or at the end of a complete antibiotic therapy course) is reasonable to reduce the risk of recurrent embolism. Delaying surgery for at least 4 weeks may be reasonable for patients with IE complicated with severe ischemic stroke or intracranial hemorrhage if the patient is hemodynamically stable.

### 1.2.3 Left Ventricular Thrombus

In patients with ischemic stroke or TIA and acute myocardial infarction (MI), whose imaging examination found left ventricular mural thrombus formation, anticoagulation with

warfarin is recommended for at least 3 months. In patients with stroke or TIA complicated with acute anterior MI with reduced ejection fraction (EF <50%) but no evidence of left ventricular thrombus, empirical anticoagulant therapy for at least 3 months can be considered to reduce the risk of cardiogenic stroke.

#### **1.2.4 Cardiomyopathy**

In patients with ischemic stroke or TIA complicated with ischemic, nonischemic, restrictive cardiomyopathy with left atrial or left atrial appendage thrombus or left ventricular dysfunction, anticoagulation with warfarin for at least 3 months is recommended to reduce the risk of recurrent stroke or TIA.

#### **1.2.5 Patent Foramen Ovale (PFO)**

In patients with a nonlacunar ischemic stroke of undetermined cause and a PFO, the decision for PFO closure versus medical management should be discussed jointly by the patient, the cardiologist, and the neurologist, considering the probability of a causal role for the PFO. In patients age 18-60 years with an unexplained nonlacunar infarction and PFO, if it is confirmed that PFO is accompanied by high-risk anatomical features after comprehensive evaluation, closure with a transcatheter device and long-term antiplatelet therapy should be considered to prevent recurrent stroke. If PFO is not accompanied by high-risk anatomical features, the benefit of transcatheter closure is uncertain.

The decision process for in-hospital antithrombotic therapy in patients with cardiogenic stroke is shown in Figure 1B. The development of in-hospital antithrombotic therapy processes in patients with cardiogenic stroke is mainly based on the following RCT evidence: ACTIVE-W, ACTIVE-A, ENGAGE AF-TIMI 48, AVERROES, ARISTOTLE, ROCKET AF, RE-LY (Table 2). [27-33]

### **2 Blood Lipid Management**

The management of blood lipids is an important core strategy for the secondary prevention of ischemic stroke. Among patients already taking statins at the time of stroke onset of noncardiogenic ischemic stroke, continuation of statin therapy during the acute period is reasonable. For patients with AIS who qualify for statin treatment, in-hospital initiation of

statin therapy is reasonable. Patients with AIS should be managed according to the 2018 ACC/AHA Cholesterol Guidelines[34], which include lifestyle modification, dietary recommendations, and medication recommendations. In patients with clinical atherosclerotic cardiovascular disease (ASCVD)  $\leq 75$  years old, if there is no contraindication, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in low-density lipoprotein cholesterol (LDL-C) levels. In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy could be chosen. In patients aged  $>75$  years with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, side effects, and drug–drug interactions, as well as patient preferences. LDL-C  $< 1.8$  mmol/l (70 mg/dl) is suggested as the target value of cholesterol-lowering therapy. In very high-risk ASCVD patients receiving the maximally tolerated dose of statins and have an LDL-C level of 1.8 mmol/L or higher ( $\geq 70$  mg/dL), it is reasonable to add ezetimibe therapy. In very high-risk ASCVD patients receiving the maximally tolerated dose of LDL-C lowering therapies and have an LDL-C 1.8 mmol/L or higher ( $\geq 70$  mg/dL) or a non-HDL-C level of 2.6 mmol/L or higher ( $\geq 100$  mg/dL), it is reasonable to add a PCSK9 inhibitor after a clinician-patient discussion about the benefit, safety, and cost. Maximally tolerated doses of LDL-C-lowering therapies should include maximally tolerated doses of statins and ezetimibe. According to cardiovascular disease management guidelines, AF cannot be the reason for not using statins in patients with ischemic stroke.[35]

The decision process for in-hospital blood lipid management in patients with AIS is shown in Figure 2, which is mainly based on the following RCT evidence: TST, SPARCL, ASSORT, IMPROVE-IT, SHARP, ODYSSEY OUTCOMES, etc. (Table 3) [36-45]

### 3 Blood Pressure (BP) Management

Patients who have elevated BP and are eligible for treatment with IV alteplase should have their BP carefully lowered so that SBP is  $<180$  mmHg and diastolic BP is  $<100$  mmHg before IV alteplase therapy is initiated and should maintain a BP  $<180/100$  mmHg for the first 24 hours after treatment. In patients undergoing mechanical thrombectomy and who have not

received IV alteplase therapy, it is reasonable to maintain BP  $\leq 180/100$  mmHg before the procedure and maintain BP  $\leq 180/105$  mmHg during the procedure and within 24 hours after the procedure. After reperfusion, SBP could be controlled below 140 mmHg. In AIS patients with comorbidities (e.g., concomitant acute coronary event, acute heart failure, aortic dissection, sICH after IV alteplase, or preeclampsia/eclampsia), early treatment of hypertension is required, and an initial BP reduction of 15% is a reasonable goal. Other patients should be managed according to these guidelines: 1) In patients with a BP  $\geq 220/120$  mmHg, it might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke; the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. 2) In patients with a BP  $< 220/120$  mmHg, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after AIS is not effective in preventing death or dependency. 3) Starting or restarting antihypertensive therapy during hospitalization in patients with BP  $> 140/90$  mmHg who are neurologically stable is safe and is reasonable to improve long-term BP control. 4) Patients with ischemic stroke who have a history of hypertension and have received antihypertensive drugs for a long time should restart antihypertensive treatment a few days after onset if there is no absolute contraindication.

In patients with hypertension complicated with stroke or TIA, treatment with a thiazide diuretic, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blockers for lowering BP is recommended to reduce the risk of recurrent stroke. A BP goal of  $< 130/80$  mmHg is recommended for most patients to reduce the risk of recurrent stroke and vascular events. Individualized drug regimens that consider patient comorbidities, classes of medications, and patient preference are recommended to maximize drug efficacy.

The decision process for in-hospital blood pressure management in patients with AIS is shown in Figure 3, which is mainly based on the following RCT evidence: ENCHANTED, RIGHT-2, ENOS, VENTURE, CATIS, SCAST, COSSACS, PRoFESS, ACCESS, RESPECT, etc. (Table 4) [46-65]

#### **4 Blood Glucose Management**

If blood glucose > 10.0 mmol/L in patients with AIS, then insulin therapy should be initiated. It is reasonable to treat hyperglycemia to achieve blood glucose levels in the range of 7.8 to 10.0 mmol/L and to closely monitor the levels to prevent hypoglycemia. If blood glucose < 3.3 mmol/L, then 10% to 20% glucose should be given orally or by injection and blood glucose levels should be monitored. In patients without a previous history of diabetes, oral glucose tolerance tests, insulin release tests and glycosylated hemoglobin A1c (HbA1c) tests should be performed after the patient's condition is stable. According to medical history and test results, the types of abnormal glucose metabolism included the following: (1) Diabetes: Lifestyle modifications such as a reasonable diet, weight control, and increased physical activity should be recommended, glucose-lowering medications should be administered, and the target value of blood glucose control is  $\text{HbA1c} \leq 7.0\%$ . (2) Insulin resistance: lifestyle modifications such as a reasonable diet, weight control, increased physical activity and medication should be administered. (3) Impaired glucose tolerance: Lifestyle intervention is necessary. Medication should be considered when necessary. (4) Impaired fasting blood glucose: Lifestyle interventions should be performed in patients with impaired fasting blood glucose, however other patients should regularly monitor blood glucose and remain alert to hypoglycemic events.

The decision process for in-hospital blood glucose management in patients with AIS is shown in Figure 5, which is mainly based on the following RCT evidence: SHINE, THIS, ADVANCE, and ACCORD (Table 4). [66-70]

## 5 Complication Management

Dysphagia is a common complication and a main risk factor for aspiration pneumonia. Therefore, effective swallowing function tests are necessary before taking oral medication or food. [71] Patients with AIS are at high risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism. For patients who are unable to walk on their own, preventive measures such as intermittent pneumatic compression (IPC) devices should be taken to reduce the risk of DVT. [72, 73] Elastic stockings are not beneficial for patients with AIS.

## 6 Etiology and Pathogenesis of Ischemic Stroke



For patients with AIS, more etiological information should be obtained through brain MRI and neck angiography. Cardiac monitoring is recommended to screen AF and other serious arrhythmias that require intervention. Reasonable use of echocardiography and high-resolution MR angiography (HR-MRA) can provide more information that guides secondary stroke prevention.

Currently, common stroke classification systems include the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and the Chinese Ischemic Stroke Subclassification (CISS).

### **6.1 TOAST Classification system**

TOAST classification is an internationally recognized etiological classification system for ischemic stroke, which includes five categories: (1) large-artery atherosclerosis (LAA), (2) cardioembolism, (3) small-artery occlusion (lacune), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology.[74]

#### ***LAA***

(1) Symptoms of cortical damage such as aphasia, neglect, impaired motor function or brainstem or cerebellar dysfunction. (2) A history of TIAs, mostly in the same arterial supply area, murmur on carotid, or diminished pulses, is helpful for clinical diagnosis. (3) Brain CT/MRI examination can find lesions in the cortical or cerebellar and brain stem or subcortical hemispheric infarcts > 1.5 cm in diameter, which may indicate ischemic stroke caused by potential large-artery atherosclerotic origin. (4) Evaluation by ultrasonography, transcranial Doppler (TCD), MR angiography (MRA), CT angiography (CTA), or digital subtraction angiography (DSA) finds more than 50% stenosis or occlusion of an appropriate intracranial or extracranial artery to support the diagnosis. (5) Potential sources of cardiogenic embolism should be excluded through relevant examinations.

#### ***Cardioembolism***

Arterial occlusions caused by a variety of heart diseases that can produce cardiogenic emboli. Cardiac sources are classified into high- and medium-risk groups based on the evidence of their relative propensities for embolism. (1) Diagnosis of possible or probable

cardioembolic stroke requires the discovery of at least one embolus of cardiac origin. (2) The clinical manifestations and brain imaging findings are similar to those found in LAA. (3) Evidence of a TIA or stroke in two or more arterial areas in the past or systemic embolism is helpful for the clinical diagnosis of cardiogenic stroke. (4) Potential large-artery atherosclerotic-derived thrombus or embolism must be excluded. (5) Patients with a medium-risk embolism of cardiac origin and no other cause of stroke are classified as having a possible cardioembolic stroke.

***Small-artery occlusion (lacune).***

(1) The patient presents with classic clinical lacunar syndromes and no evidence of cerebral cortical dysfunction. (2) A history of diabetes mellitus or hypertension is helpful for the clinical diagnosis. (3) A normal brain CT/MRI examination or a lesion with a diameter of <1.5 cm in the relevant brain stem or subcortical hemisphere is found. (4) Potential embolisms of cardiac origin were excluded. (5) The stenosis of the ipsilateral large extracranial artery of the lesion should not exceed 50%.

***Stroke of other determined etiology.***

This category is a rare cause of ischemic stroke, such as acute cerebral infarction caused by infectious, immune, nonimmune vascular diseases, hypercoagulable states, hematological system diseases, hereditary vascular diseases and drug abuse. Patients in this category should have clinical and CT or MRI scans of an AIS, regardless of the size or location. Diagnostic examinations such as blood tests or arteriography can be helpful in finding one of these unusual causes of stroke. Cardiac origin embolism and LAA should be excluded by other examinations.

***Stroke of undetermined etiology.***

This subtype is further divided into the following. (1) Two or more plausible causes are found so that the physician is unable to make a final diagnosis. (2) The etiology is still uncertain despite a comprehensive evaluation. (3) No cause was found, but the assessment was cursory.

The decision process of the TOAST classification is shown in Figure 5A.

## 6.2 CISS Classification system

The CISS is the most suitable classification system for the etiology and pathogenesis of ischemic stroke in the Chinese population. The CISS includes five categories of stroke types: (1) large artery atherosclerosis, (2) cardiogenic stroke, (3) penetrating artery disease, (4) other etiologies and (5) undetermined etiology. [75]

### *Large artery atherosclerosis (LAA)*

LAA is often accompanied by risk factors such as smoking, hypertension, diabetes, hyperlipidemia, and other risk factors. According to the location, LAA divides into aortic arch atherosclerosis and intra/extracranial large atherosclerosis

#### (1) Aortic arch atherosclerosis

1) Acute multiple infarct lesions, especially involving bilateral anterior and/or anterior and posterior circulations; 2) Without evidence of corresponding intracranial or extracranial large artery (vulnerable plaques or stenosis  $\geq 50\%$  or occlusion) atherosclerosis; 3) Evidence of aortic arch atherosclerosis with underlying etiology (aortic plaques  $\geq 4$  mm and/or aortic thrombi, detected by HR-MRI/MRA and/or transesophageal echocardiography); 4) Cardiogenic stroke was excluded; 5) Other possible causes, such as vasculitis and tumor embolism, were excluded.

#### (2) Intra- and extracranial large artery atherosclerosis

1) Evidence of corresponding intracranial or extracranial large arteries (vulnerable plaques or stenosis  $\geq 50\%$ ) atherosclerosis, regardless of the type of infarction (except the isolated infarction in the penetrating artery area); 2) Isolated infarction in the penetrating artery area 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) Cardiogenic stroke needs to be excluded; 4) Other possible causes are excluded.

In the CISS system, the underlying mechanisms of ischemic stroke caused by intracranial or extracranial LAA are further divided into four subtypes:

(1) Parent artery (plaque or thrombus) occluding penetrating: Acute isolated infarct in the distribution area of penetrating artery with evidence of plaque or any degree of stenosis in the parent artery.

(2) Artery-to-artery embolism: Imaging shows small cortical infarcts or a single regional infarct in the area provided by the associated intracranial or extracranial artery atherosclerosis.

(3) Hypoperfusion/reduced emboli clearance: Acute infarcts occur in the watershed area. The degree of intracranial or extracranial artery stenosis corresponding to clinical symptoms is usually >70%.

(4) Multiple mechanisms: Two or more underlying mechanisms mentioned above coexist.

### ***Cardiogenic stroke (CS)***

Cerebral embolism is caused by many kinds of diseases that can produce cardiac embolus.

(1) Acute multiple infarcts, especially those involving bilateral anterior and/or anterior and posterior circulations (including cortical infarcts) that have happened closely in time; (2) Evidence of cardiogenic stroke; (3) No evidence of corresponding intracranial or extracranial large arteries atherosclerosis; (4) Other causes are excluded; (5) If the possibility of aortic arch atherosclerosis has ruled out, CS is definite. Otherwise, it is considered a possible CS.

Evidence of CS includes (a) mitral stenosis; (b) prosthetic heart valve; (c) myocardial infarction within the past 4 weeks; (d) left ventricular mural thrombus; (e) left ventricular aneurysm; (f) AF or flutter; (g) sick sinus syndrome; (h) dilated cardiomyopathy; (i) ejection fraction <35%; (j) endocarditis; (k) intracardiac mass; (l) PFO with in situ thrombosis; and (m) PFO with PE or DVT before cerebral infarction.

### ***Penetrating artery disease (PAD)***

Acute isolated infarction in the area of one penetrating artery due to atherosclerosis at the proximal segment of the penetrating arteries or lipohyalinotic degeneration of arterioles is called PAD.

(1) Acute isolated infarction in the area of one penetrating artery corresponding to clinical symptoms, regardless of infarct size; (2) Parent artery without atherosclerotic plaque (detected by HR-MRI) or any degree of stenosis (detected by TCD, MRA, CTA, or DSA); (3) No evidence of vulnerable plaques or stenosis >50% in the corresponding ipsilateral proximal intracranial or extracranial large arteries; (4) Excluding cardioembolic stroke; (5) Excluding other etiologies.

#### ***Other etiologies (OE)***

Evidence of other specific diseases related to the index stroke and the possibility of LAA or CS was excluded.

#### ***Undetermined etiology (UE)***

No cause was found to explain the index stroke.

(1) Multiple: More than two etiologies have been found, but it is difficult to determine which one was related to the index stroke.

(2) Unknown: No definite cause is found, or there is a suspicious cause, but more investigations would be performed.

(3) Inadequate examination: Routine intracranial and extracranial arteries or heart examinations have not been completed, making it difficult to determine the etiology.

The decision process of the CISS classification is shown in Figure 5B.

TABLE 1. RCTs of Antithrombotic Therapy for Noncardiogenic Stroke.

Study Acronym: Year Published	Aim of Study	Conclusions
CHANCE-2, 2021, PMID: 34708996[25]	To test the hypothesis that ticagrelor combined with aspirin is superior to clopidogrel combined with aspirin in reducing the risk of recurrence in patients with a minor ischemic stroke or TIA who carry CYP2C19 loss-of-function alleles.	Among Chinese patients with minor ischemic stroke or TIA who were carriers of CYP2C19 loss-of-function alleles, the risk of stroke at 90 days was modestly lower with ticagrelor than with clopidogrel. The risk of severe or moderate bleeding did not differ between the two treatment groups, but ticagrelor was associated with more total bleeding events than clopidogrel.
THALES, 2020, PMID: 32668111[26]	To Assess the effect of the combination of ticagrelor and aspirin on stroke prevention.	Among patients with a mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS $\leq 5$ ) or TIA who were not undergoing intravenous or endovascular thrombolysis, the risk of the composite of stroke or death within 30 days was lower with ticagrelor-aspirin than with aspirin alone. Severe bleeding was more frequent in patients taking ticagrelor.
PRINCE, 2019, PMID: 31171523[4]	To test the hypothesis that ticagrelor plus aspirin is safe and superior to clopidogrel plus aspirin for reducing high platelet reactivity at 90 days and stroke recurrence in patients with minor stroke or TIA, particularly in carriers of the CYP2C19 loss-of-function allele and patients with large artery atherosclerosis.	Patients with minor stroke or transient ischemic attack who are treated with ticagrelor plus aspirin have a lower proportion of high platelet reactivity than those who are treated with clopidogrel plus aspirin, particularly for those who are carriers of the CYP2C19 loss-of-function allele.
POINT, 2018, PMID: 29766750[5]	To evaluate whether the combination of clopidogrel and aspirin can reduce the risk of composite vascular events in an international population of patients with acute high-risk TIA or mild	In patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin within 12 hours after onset had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90

	ischemic stroke compared with aspirin alone.	days than those who received aspirin alone.
SOCRETS, 2016, PMID: 27160892[6]	To compare the effects of ticagrelor with aspirin on the prevention of major vascular events (a composite of stroke [ischemic or hemorrhagic], myocardial infarction, or death) over a period of 90 days in patients with acute cerebral ischemia.	In patients with AIS or TIA, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days.
SAMMPRIS, 2014, PMID: 24168957[7]	To assess whether percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical treatment is more effective than aggressive medical treatment alone on intracranial arterial stenosis in high-risk patients.	The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with severe intracranial stenosis.
CHANCE, 2013, PMID: 23803136 [8]	To test the hypothesis that 3 months of treatment with a combination of clopidogrel and aspirin compared with aspirin alone would reduce the risk of recurrent stroke among patients with minor ischemic stroke or high-risk TIA.	Among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage.
SPS3, 2012, PMID: 22931315[9]	To compare the efficacy and safety of clopidogrel combined with aspirin in patients with symptomatic lacunar stroke within 6 months.	Among patients with recent lacunar strokes, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke and did significantly increase the risk of bleeding and death.
SaTIS, 2011, PMID: 21852609[10]	To evaluate the safety of tirofiban in AIS patients.	Tirofiban is safe for AIS.
CSPS2, 2010,	To compare the efficacy and safety of cilostazol and aspirin for secondary prevention of ischemic	Compared with aspirin, cilostazol reduced the risk of stroke recurrence, caused less bleeding, but increased

PMID: 20833591[11]	stroke; -	adverse events such as dizziness and palpitations
CLAIR, 2010, PMID: 20335070[12]	To investigate whether treatment with clopidogrel plus aspirin reduced the number of microembolic signals detected with transcranial doppler ultrasound compared with aspirin alone in patients with recent stroke.	Combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with predominantly intracranial symptomatic stenosis.
PRoFESS, 2008, PMID: 18753638[13]	To compare the efficacy and safety of aspirin plus extended-release dipyridamole (ASA-ERDP) and clopidogrel in patients with ischemic stroke within 90 days.	In patients with ischemic stroke within 90 days after onset, the efficacy of ASA-ERDP was similar to that of clopidogrel alone, but the major hemorrhagic events and intracranial hemorrhage increased significantly.
CASISP, 2008, PMID: 18456558[14]	To compare the efficacy and safety of cilostazol with that of aspirin for the long-term (1-6 months) prevention of the recurrence of ischemic stroke.	In patients with ischemic stroke for 1-6 months, cilostazol tended to reduce the relative risk of stroke recurrence compared with aspirin, but there was no significant difference. Lower rates of ischemic and hemorrhagic stroke were observed in the cilostazol group.
ABESTT-II, 2008, PMID: 18032739[15]	To test the efficacy and safety of abciximab in patients with AIS within 5 hours after symptoms onset.	Intravenous administration of abciximab did not improve functional prognosis, but increased the risk of intracranial hemorrhage.
FASTER, 2007, PMID: 17931979[16]	To assess whether initiation of simvastatin within 24 hours of symptom onset for 90 days reduces the risk of stroke recurrence in TIA and minor stroke.	Immediately after TIA or minor stroke, using clopidogrel in addition to aspirin showed a trend of reduced risk of 90-day stroke and composite events compared with aspirin alone, but there was no significant difference.
ESPRIT, 2006, PMID: 16714187[17]	To compare the efficacy and safety of aspirin combined with dipyridamole versus aspirin alone for the secondary prevention of vascular events after ischemic stroke of putative arterial origin	The combination regimen of aspirin plus dipyridamole as antithrombotic therapy can reduce the risk of composite events compared with aspirin alone after cerebral ischemia of arterial origin.
CARESS,	To evaluate whether clopidogrel in combination with aspirin is superior	In patients with recently symptomatic carotid stenosis, combination therapy



2005, PMID: 15851601[18]	to aspirin alone in reducing the incidence of microembolic signals detected by Transcranial Doppler in patients with recently symptomatic carotid stenosis.	with clopidogrel and aspirin is more effective than aspirin alone in reducing asymptomatic embolization.
MATCH, 2004, PMID: 15276392 [19]	To assess whether the addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in the prevention of vascular events with a potentially higher bleeding risk.	Adding aspirin to clopidogrel in high-risk patients with recent ischemic stroke or TIA is associated with a nonsignificant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding is increased by the addition of aspirin.
IST, 1997, PMID: 9174558[20]	To provide reliable evidence on the safety and efficacy of aspirin and of subcutaneous heparin.	Aspirin can be used in the treatment of AIS to reduce all-cause mortality and stroke recurrence rate.
CAST, 1997, PMID: 9186381[21]	To evaluate the efficacy and safety of early aspirin use in patients with acute ischemic stroke.	Early aspirin can be used in the treatment of AIS to reduce all-cause mortality and stroke recurrence rate.
CAPRIE, 1996, PMID: 8918275[22]	To compare the efficacy and safety of clopidogrel with aspirin in in reducing the risk of a composite outcome cluster of ischemic stroke, myocardial infarction, or vascular death.	Long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death. The overall safety profile of clopidogrel is at least as good as that of medium-dose aspirin.
ESPS II, 1995 PMID: 24283721[23]	To examine the relative roles of aspirin and dipyridamole alone and in combination on secondary prevention, evaluate the efficacy of small doses of aspirin and verify antiplatelet efficacy in complete stroke patients.	Aspirin plus dipyridamole can reduce the recurrence risk of ischemic stroke compared with placebo or aspirin alone and increase the risk of bleeding.

Table 2. RCTs of Antithrombotic Therapy for Cardiogenic Stroke.

Study Acronym; Year Published	Aim of Study	Conclusions
ACTIVE-A, 2009, PMID: 19336502[27]	To evaluate the efficacy and safety of clopidogrel plus aspirin compared with aspirin alone in AF patients who are unsuitable for oral anticoagulation therapy (vitamin K-antagonist).	In AF patients who are unsuitable for vitamin K-antagonist therapy, the addition of clopidogrel to aspirin reduces the risk of major vascular events, especially stroke, and increases the risk of major hemorrhage.
ACTIVE-W, 2006, PMID: 16765759[28]	To assess whether clopidogrel plus aspirin was noninferior to oral anticoagulation therapy in preventing vascular events in AF patients with at least one risk factor.	Oral anticoagulation therapy is superior to clopidogrel plus aspirin for preventing vascular events in AF patients at high risk of stroke, especially in those already taking oral anticoagulation therapy
<b>NOACs</b>		
ENGAGE AF-TIMI 48, 2013, PMID: 24251359[29]	To compare the efficacy of edoxaban and warfarin in patients with moderate-to-high-risk AF.	Edoxaban is noninferior to warfarin with respect to the prevention of stroke or systemic embolism and is associated with significantly lower rates of bleeding and death from cardiovascular causes.
AVERROES, 2011, PMID: 21309657[30]	To evaluate the efficacy and safety of apixaban (5 mg bid) in patients with AF whom vitamin K antagonist therapy was unsuitable.	In patients with AF for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke and systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.
ARISTOTLE, 2011, PMID:21870978[31]	To investigate whether apixaban is superior to warfarin in reducing the risk of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke.	In patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.
ROCKET AF, 2011,	To compare the efficacy of rivaroxaban and dose adjusted warfarin for the prevention of stroke or systemic embolism in	In patients with AF, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant

PMID:21830957[32]	patients with nonvalvular AF.	between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
RE-LY, 2009, PMID: 19717844[33]	To compare the efficacy between two doses of dabigatran and adjusted-dose warfarin for the prevention of stroke or systemic embolism in patients with AF.	In patients with AF, dabigatran given at a dose of 110 mg was associated with low rates of stroke and systemic embolism, which were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

Table 3. RCTs of In-hospital Blood Lipid Management in Patients with AIS

Study Acronym; Year Published	Aim of Study	Conclusions
TST, 2020, PMID: 31738483 <sup>65</sup>	To test the hypothesis that a target level of LDL-C of less than 70 mg per deciliter would be superior to a target range of 90 mg to 110 mg per deciliter in reducing overall cardiovascular events after an ischemic stroke or a TIA in patients with evidence of atherosclerosis.	After an ischemic stroke or TIA with evidence of atherosclerosis, patients who had a target LDL-C level of less than 1.8 mmol/L had a lower risk of subsequent cardiovascular events than those who had a target range of 90 mg to 110 mg per deciliter.
ASSORT, 2017, PMID: 29030478[37]	To evaluate the effect of early versus delayed statin therapy in patients with AIS.	The trial did not show any superiority of early statin therapy in alleviating the degree of disability at 90 days after onset in AIS patients with dyslipidemia within 24 hours of admission compared with delayed statin therapy 7 days after admission.
FASTER, 2007, PMID: 17931979[38]	To assess whether initiation of simvastatin within 24 hours of symptom onset for 90 days reduces the risk of stroke recurrence in TIA and minor stroke patients.	There was no significant difference in stroke recurrence or safety endpoint between simvastatin and placebo groups; Insufficient research effectiveness due to early termination; The dosage of statins is moderate (not recommended for high-intensity statins in secondary prevention of stroke).
Blanco M,et al. 2007, PMID: 17724294[39]	To investigate the influence of statin pretreatment and its withdrawal on outcomes in AIS patients.	Statin withdrawal is associated with increased risk of death or dependency at 90 days.
SPARCL, 2006, PMID: 16899775[40]	To determine whether a daily dose of 80 mg of atorvastatin would reduce the risk of stroke in patients with no known coronary heart disease who had had a stroke or TIA within the previous six months.	In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke.
<b>Ezetimibe Added to Statin Therapy</b>		

IMPROVE-IT, 2015, MID: 26039521[41]	To determine whether the addition of ezetimibe, as compared with that of simvastatin alone, in stable patients who had had an acute coronary syndrome and whose LDL -C values were within guideline recommendations.	Ezetimibe added to moderate-intensity statin therapy resulted in incremental lowering of LDL-C and improved cardiovascular outcomes. Moreover, lowering LDL -C to levels below previous targets provided additional benefit.
SHARP, 2011, PMID: 21663949[42]	To assess the efficacy and safety of the combination of simvastatin plus ezetimibe in patients with advanced chronic kidney disease.	Reduction of LDL-C with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.
SEAS, 2008, PMID: 18765433[43]	To study the effects of long-term, intensive cholesterol lowering with daily use of simvastatin and ezetimibe on clinical and echocardiographic outcomes in patients with asymptomatic, mild-to-moderate aortic-valve stenosis and no other indication for lipid-lowering treatment.	Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis
<b>PCSK9 in Cholesterol-lowering Therapy</b>		
ODYSSEY OUTCOMES, 2018, PMID: 30403574[44]	To determine whether alirocumab, a human monoclonal antibody to PCSK9, would reduce the risk of recurrent ischemic cardiovascular events among patients who had an acute coronary syndrome within the preceding 1 to 12 months and who have levels of atherogenic lipoproteins that exceed specified thresholds despite statin therapy at a high-intensity dose or at the maximum tolerated dose.	Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo.
FOURIER, 2017,	To test the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular	Evolocumab added to high-intensity or moderate-intensity statin therapy lowered LDL-C levels to a median of 30 mg per deciliter and reduced the risk of cardiovascular events among patients with atherosclerotic

PMID: 28304224 <sup>[45]</sup>	disease.	cardiovascular disease.
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Table 4. RCTs of In-hospital Blood Pressure Management in Patients with AIS.

Study Acronym; Year Published	Aim of Study	Conclusions
<b>RCTs of Antihypertensive Therapy in patients with intravenous thrombolysis</b>		
ENCHANTED, 2019, PMID: 30739745[46]	To assess intensive blood pressure lowering therapy compared with guideline-recommended blood pressure lowering therapy in patients treated with alteplase for AIS.	Although intensive blood pressure lowering therapy is safe, it cannot improve clinical outcomes in patients treated with alteplase for AIS.
<b>RCTs Comparing Early Versus Delayed Initiation of Treatment for Blood Pressure Reduction in Patients with AIS</b>		
RIGHT-2, 2019, PMID: 30738649[47]	To investigate whether transdermal glyceryl trinitrate improves outcomes when administered very early after stroke onset.	Prehospital treatment with transdermal glyceryl trinitrate does not seem to improve functional outcomes in patients with presumed stroke. It is feasible for UK paramedics to obtain consent and treat patients with stroke in the ultra-acute prehospital setting.
ENOS, 2015, PMID: 25465108[48]	To assess the safety and efficacy of glyceryl trinitrate, when given within 48 h, in patients with acute ischemic or hemorrhagic stroke and high blood pressure, and to assess the outcomes of a subset of patients who continued or stopped taking antihypertensive drugs for 1 week after their stroke.	In patients with acute stroke and high blood pressure, transdermal glyceryl trinitrate lowered blood pressure and had acceptable safety but did not improve functional outcomes. We show no evidence to support continuing prestroke antihypertensive drugs in patients in the first few days after acute stroke.
VENTURE, 2015, PMID: 25580869[49]	To assess the efficacy and safety of modest blood pressure reduction with valsartan within the first 24 to 48 h of an ischemic stroke.	Early reduction in BP with valsartan did not reduce death, dependency or major vascular events at 90 d but increased the risk of early neurological

		deterioration.
CATIS, 2014, PMID: 24240777[50]	To evaluate whether immediate blood pressure reduction in patients with AIS would reduce death and major disability at 14 days or at hospital discharge.	Among patients with AIS, BP reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce the likelihood of death or major disability at 14 days or at hospital discharge.
SCAST, 2011, PMID: 21316752[51]	To examine whether blood-pressure lowering treatment with candesartan is beneficial in a wide range of patients with acute stroke and elevated BP.	There was no indication that careful use of BP lowering treatment with candesartan, an angiotensin-receptor blocker, is beneficial in patients with acute stroke and elevated BP. If anything, the evidence suggested a harmful effect.
COSSACS, 2010, PMID: 20621562[52]	To assess the efficacy and safety of continuing or stopping preexisting antihypertensive drugs in patients with acute stroke.	Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate, or mortality at 6 months. Lower BP levels in those who continued antihypertensive treatment after acute mild stroke were not associated with an increase in adverse events.
PRoFESS, 2009, PMID: 19797187[53]	To assess the safety and efficacy of telmisartan on lowering BP (in addition to standard poststroke antihypertensive treatment) in patients with AIS.	Treatment with telmisartan in patients with acute mild ischemic stroke and mildly elevated BP appeared to be safe with no excess in adverse events, was not associated with a significant effect on functional dependency, death or recurrence, and modestly lowered BP
CHHIPS, 2009, PMID: 19058760[54]	To assess the feasibility, safety, and effects of labetalol and lisinopril on lowering BP in patients with acute stroke.	Labetalol and lisinopril are effective antihypertensive drugs that do not increase the rate of serious adverse events in acute stroke patients. Early lowering of BP with lisinopril and labetalol



		after acute stroke seems to be a promising approach to reducing mortality and potential disability.
Eveson DJ,et al. 2007, PMID: 17324738[55]	Explore the hemodynamic effect and safety of oral lisinopril initiated within 24 h after an acute stroke.	Even in small dosages, lisinopril is well tolerated and effective after AIS because it gradually reduces BP 4 h after the first oral dose.
ACCESS, 2003, PMID: 12817109[56]	Assess the safety of modest BP reduction by candesartan cilexetil in the early treatment of stroke.	Early neurohumoral inhibition has similar beneficial effects in cerebral and myocardial ischemia. A cardiovascular or cerebrovascular event that does not occur as a result of hypotension is of significant clinical importance. Candesartan cilexetil is a safe therapeutic option when needed or in cases without contraindications against early antihypertensive therapy.
VENUS, 2001, PMID: 11157183[57]	To test the hypothesis that early treatment with nimodipine has a positive effect on survival and functional outcomes after stroke.	The results of VENUS do not support the hypothesis of a beneficial effect of early treatment with nimodipine in stroke patients.
Kaste M,et al. 1994, PMID: 8023348[58]	To test the hypothesis that nimodipine would improve functional outcomes in patients with acute ischemic hemispheric stroke	Nimodipine did not improve functional outcomes in patients with acute ischemic hemispheric stroke. The early case-fatality rate was higher in the nimodipine group, possibly due to the BP lowering effect of nimodipine
<b>RCTs Comparing Blood Pressure Targets for Stroke Prevention</b>		
RESPECT, 2019 PMID: 31355878[59]	To evaluate whether intensive BP control can reduce recurrent stroke compared with standard BP control.	Intensive BP lowering therapy tended to reduce stroke recurrence. The updated meta-analysis supports a target BP less than 130/80 mm Hg in secondary stroke prevention.
PODCAST,	To assess the effect of	In patients with recent stroke and

2017, PMID: 28095412[60]	intensive BP and/or lipid lowering therapy on cognitive outcomes in patients with recent stroke.	normal cognition, intensive BP and lipid lowering were feasible and safe, but did not alter cognition over two years.
PAST-BP, 2016 PMID: 26919870[61]	To assess whether using intensive BP targets lead to lower BP in a population with prevalent cerebrovascular disease.	Aiming for a target below 130 mm Hg rather than below 140 mm Hg for systolic BP in people with cerebrovascular disease receiving primary care leads to a small additional reduction in BP. Active management of systolic BP in this population using a <140 mm Hg target led to a clinically important reduction in BP.
SPRINT, 2015, PMID: 26551272[62]	To evaluate the efficacy of intensive BP lowering therapy on lowering BP in hypertensive patients without diabetes.	Intensive BP lowering therapy can reduce the risk of fatal and nonfatal major cardiovascular events and death from any cause in high-risk cardiovascular disease patients without diabetes, although significantly higher rates of some adverse events were observed in the intensive-treatment group.
SPS3, 2013, PMID: 23726159[63]	To investigate the effect of different BP targets on the rate of recurrent stroke in patients with recent lacunar stroke.	In patients with recent lacunar stroke, the use of a systolic-blood-pressure target of less than 130 mm Hg is likely to be beneficial.
ACCORD, 2010, PMID: 20228401[64]	To investigate whether therapy that targets normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.	In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic BP of less than 120 mm Hg, compared to less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.
PATS, 1995, PMID: 8575241[65]	To determine whether antihypertensive treatment could reduce the risk of fatal and nonfatal stroke incidence	In patients with a history of stroke or TIA, BP reduction of 5/2 mmHg with 2.5 mg indapamide reduced the first

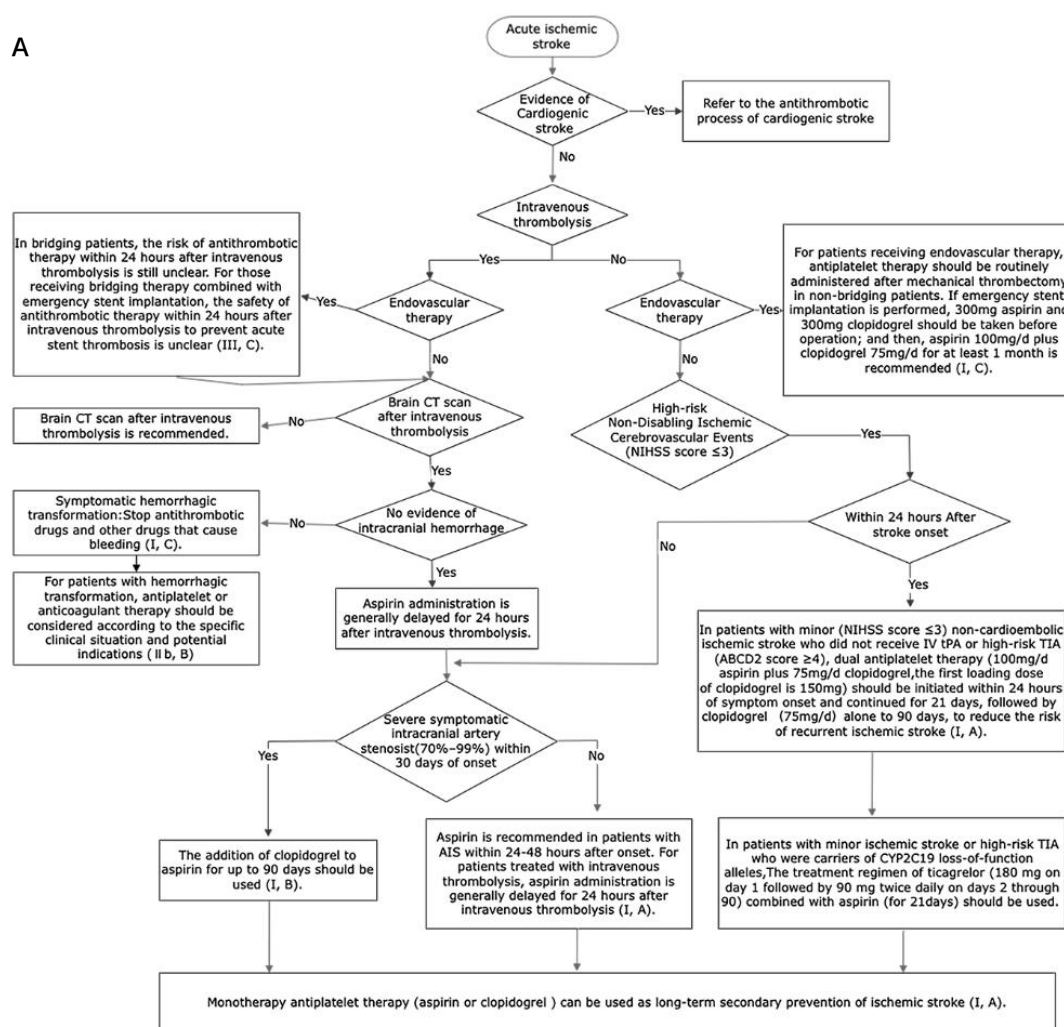
	in patients with a history of stroke or transient ischemic attack.	incidence of fatal and nonfatal stroke by 29%, with three-year absolute benefit of 29 events per 1000 participants.
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Table 5. RCTs of In-hospital Blood Glucose Management in Patients with AIS.

Study Acronym; Year Published	Aim of Study	Conclusions
SHINE, 2019, PMID: 31334795[66]	To evaluate the efficacy of intensive treatment for hyperglycemia in AIS.	Among AIS patients with hyperglycemia, treatment with intensive vs. standard glucose control for up to 72 hours did not result in a significant difference in favorable functional outcomes at 90 days.
THIS, 2008, PMID: 18096840[67]	To test the feasibility and tolerability of aggressive hyperglycemia correction with intravenous insulin compared with usual care for acute cerebral infarction.	The intravenous insulin protocol was significantly more effective in correcting hyperglycemia during acute cerebral infarction than usual care, did not result in any major adverse events and should be investigated in a clinical efficacy trial.
ADVANCE, 2008, PMID: 18539916 [68]	To assess the effect of lowering the glycated hemoglobin value to a target of 6.5% or less on major vascular outcomes in a broad cross-section of patients with type 2 diabetes.	A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as needed, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.
ACCORD, 2008, PMID: 18539917[69]	To investigate whether a therapeutic strategy that targets normal glycated hemoglobin levels (i.e., below 6.0%) would reduce the rate of cardiovascular events, as compared with a strategy that targets glycated hemoglobin levels from 7.0 to 7.9% in middle-aged and older people with type 2 diabetes mellitus and an established cardiovascular disease or an additional cardiovascular risk factor.	The use of intensive hypoglycemic therapy to target normal glycated hemoglobin levels for 3.5 years showed an increase in mortality and did not significantly reduce major cardiovascular events compared with standard therapy.

GIST-U, 2007, PMID: 17434094[70]	To determine whether treatment with glucose-potassium-insulin (GKI) infusions can maintain euglycemia immediately after the acute event or reduce 90-day mortality.	GKI infusions significantly reduced plasma glucose concentrations, but it was not associated with significant clinical benefit.
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A



**Figure 1** The decision process for in-hospital antithrombotic therapy in AIS

A. The decision process for in-hospital antithrombotic therapy in patients with noncardiogenic stroke

B

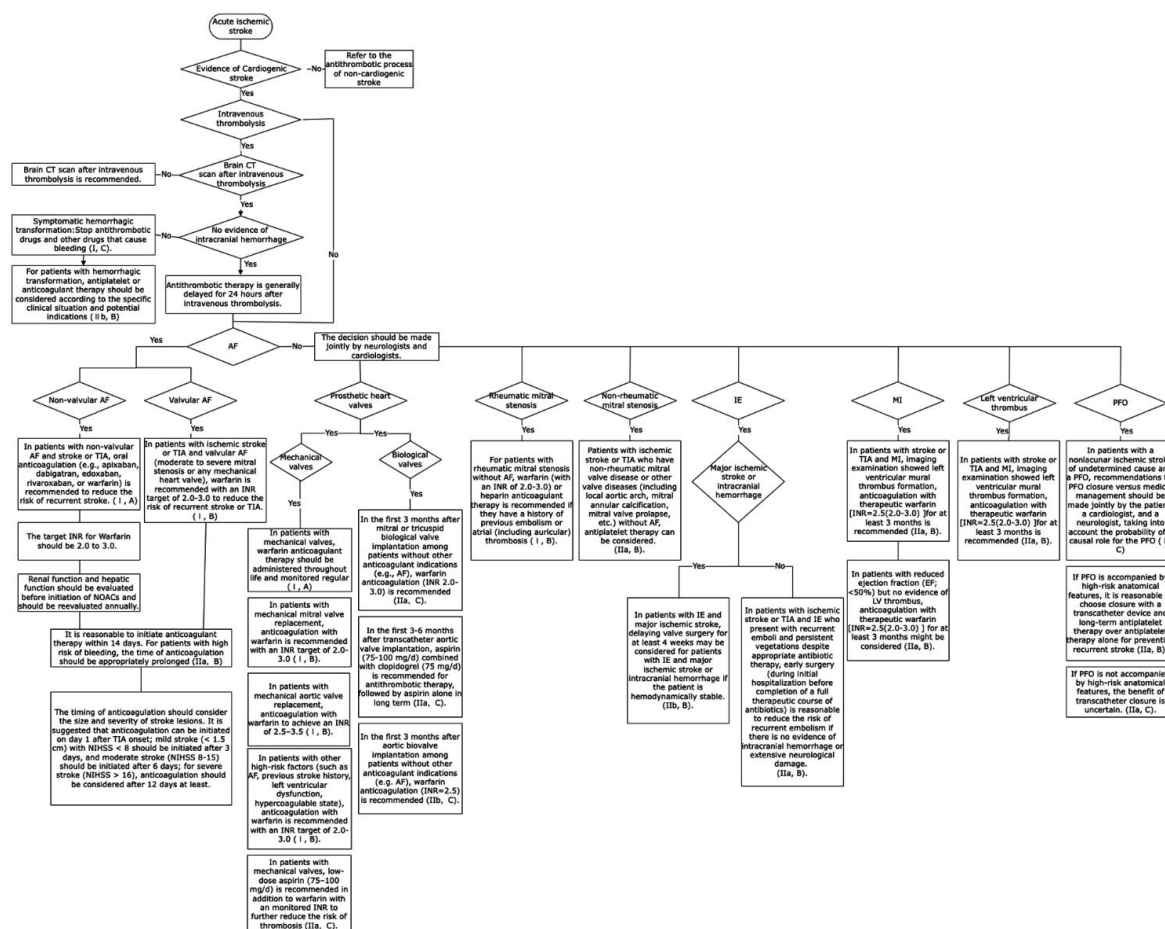


Figure 1 The decision process for in-hospital antithrombotic therapy in AIS

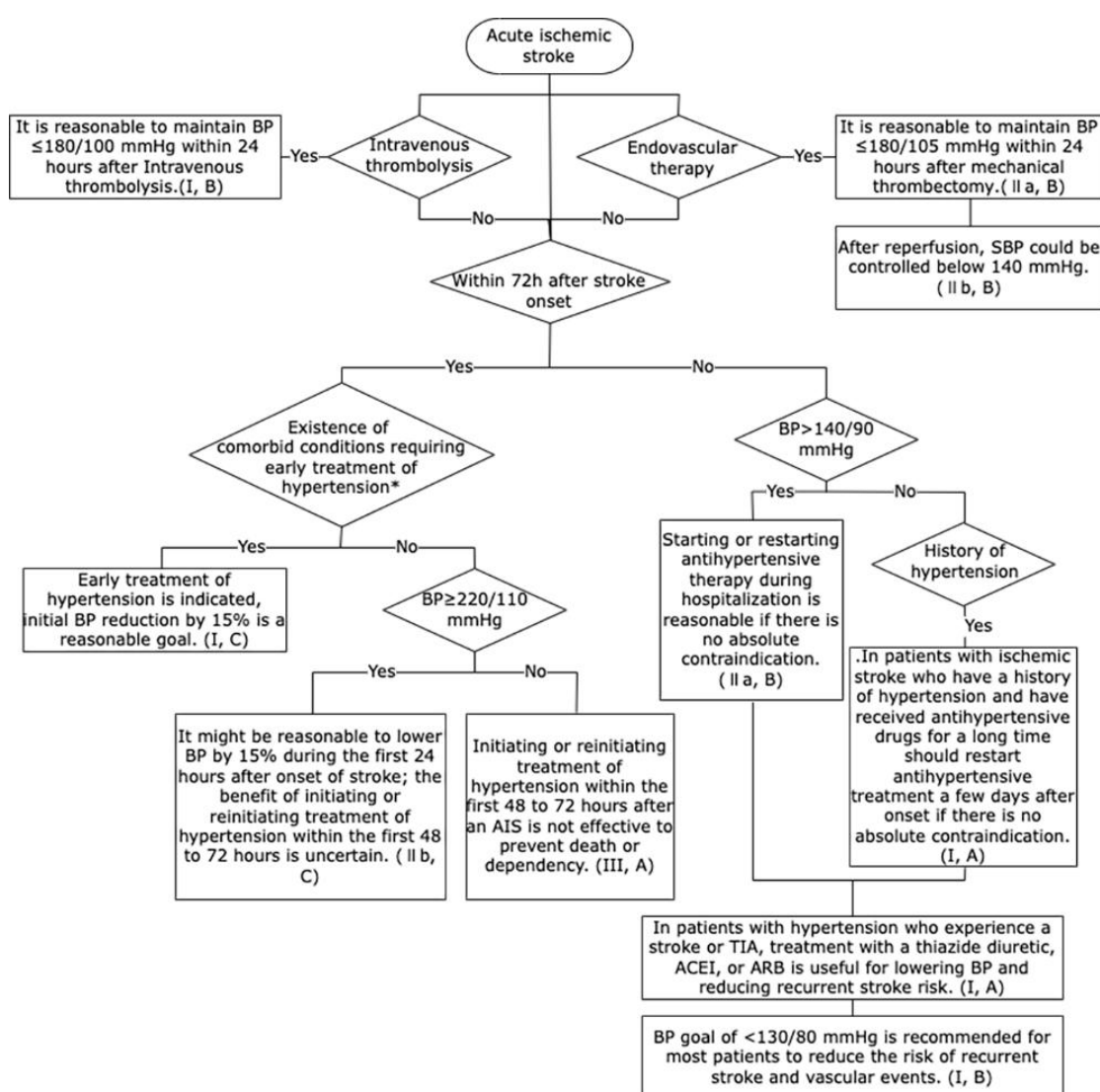
B. The decision process for in-hospital antithrombotic therapy in patients with cardiogenic stroke





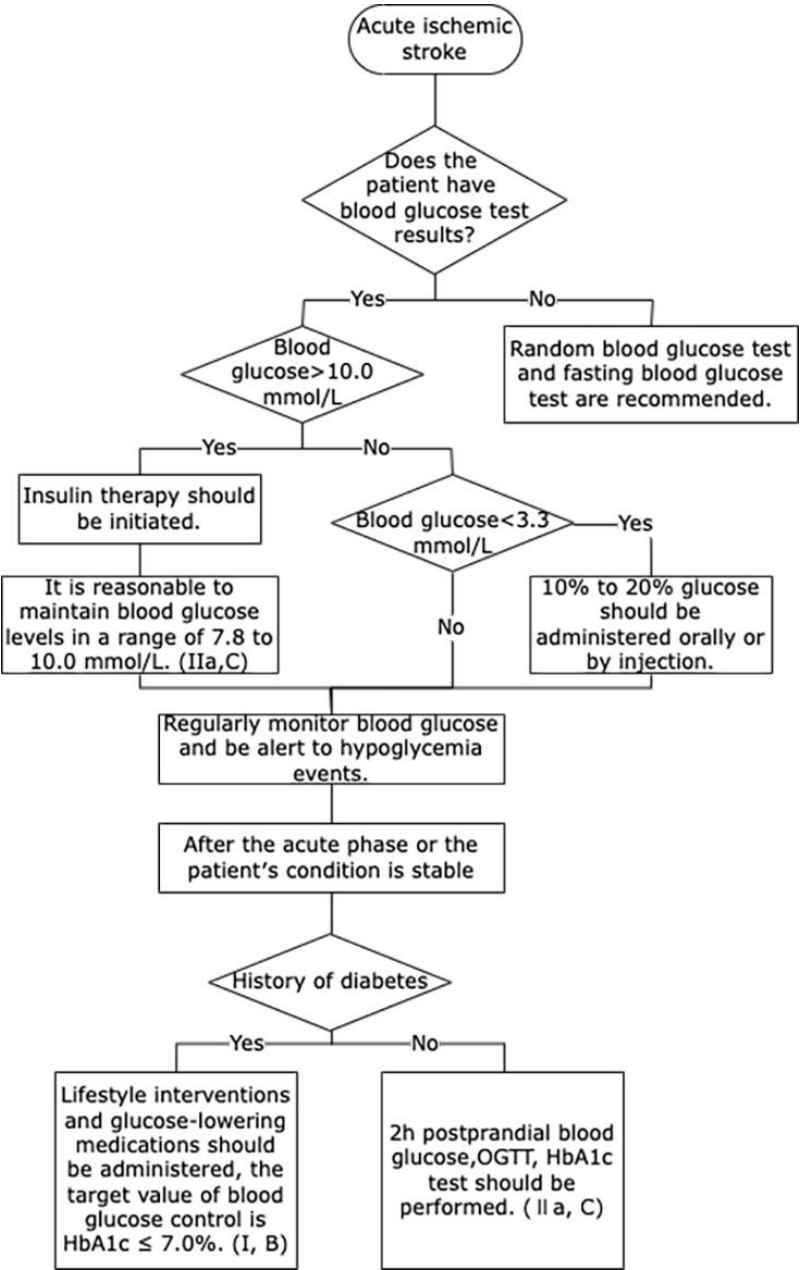
• Heterozygous familial hypercholesterolemia
• History of prior coronary artery bypass surgery or percutaneous coronary intervention
• Diabetes mellitus
• Hypertension
• CKD [eGFR 15~59 ml/ (min • 1.73 m <sup>2</sup> ) ]
• Smoking
• Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite
• maximal toleration of cholesterol lowering therapy with statins and ezetimibe
• History of congestive heart failure

ABI, ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.



**Figure 3.** The decision process for in-hospital blood pressure management in AIS patients

\* Comorbid conditions requiring early treatment of hypertension including acute coronary event, acute heart failure, aortic dissection, postfibrinolysis sICH, or preeclampsia/eclampsia



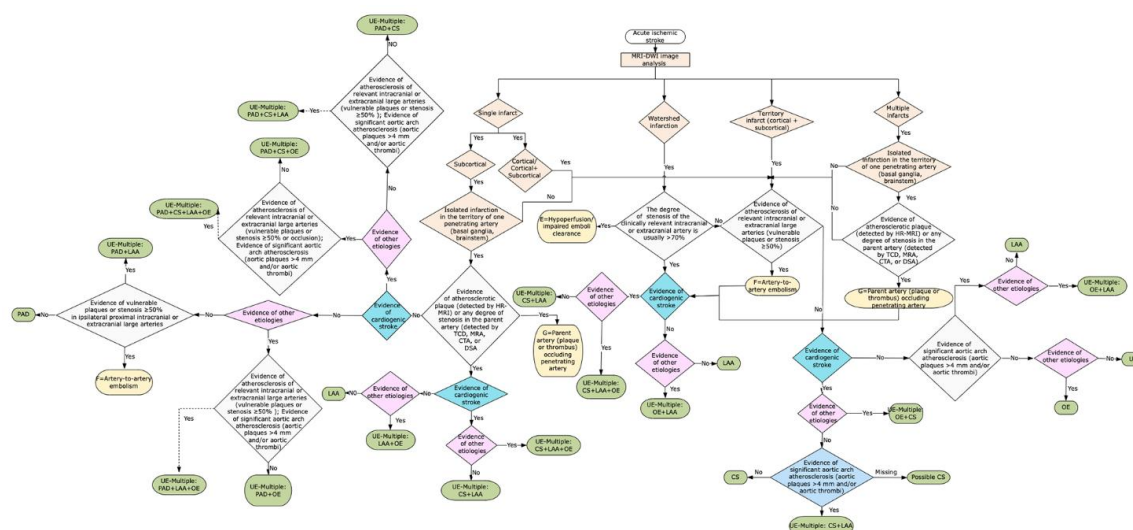
**Figure 4** The decision process for in-hospital blood glucose management in AIS patients

\* OGTT, oral glucose tolerance test





**Figure 5.** The Decision Process for the Etiology and Mechanism of AIS

A. The Decision Process for TOAST Classification.



**Figure 5.** The Decision Process for the Etiology and Mechanism of AIS

## B. The Decision Process for CISS Classification.

\*  infers judgment conditions;  infers the output (Light yellow represents the mechanism, light green represents the etiology, and the mechanism is output only when the etiology meets LAA at the same time).

**Reference:**

- [1] Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. *Circulation*. 2017;135(8):759-71.
- [2] Collaborators GBDS. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(5):439-58.
- [3] Yu F, Liu X, Yang Q, Fu Y, Fan D. In-hospital recurrence in a Chinese large cohort with acute ischemic stroke. *Sci Rep*. 2019;9(1):14945.
- [4] Wang Y, Chen W, Lin Y, Meng X, Chen G, Wang Z, et al. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. *BMJ*. 2019;365:l2211.
- [5] Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med*. 2018;379(3):215-25.
- [6] Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med*. 2016;375(1):35-43.
- [7] Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet*. 2014;383(9914):333-41.
- [8] Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369(1):11-9.
- [9] Investigators SPS, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med*. 2012;367(9):817-25.
- [10] Siebler M, Hennerici MG, Schneider D, von Reutern GM, Seitz RJ, Rother J, et al. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. *Stroke*. 2011;42(9):2388-92.
- [11] Shinohara Y, Katayama Y, Uchiyama S, Yamaguchi T, Handa S, Matsuoka K, et al. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9(10):959-68.
- [12] Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9(5):489-97.
- [13] Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359(12):1238-51.
- [14] Huang Y, Cheng Y, Wu J, Li Y, Xu E, Hong Z, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. *Lancet Neurol*. 2008;7(6):494-9.
- [15] Adams HP, Jr., Effron MB, Torner J, Davalos A, Frayne J, Teal P, et al. Emergency

- administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). *Stroke*. 2008;39(1):87-99.
- [16] Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6(11):961-9.
- [17] Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367(9523):1665-73.
- [18] Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation*. 2005;111(17):2233-40.
- [19] Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331-7.
- [20] The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet*. 1997;349(9065):1569-81.
- [21] CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet*. 1997;349(9066):1641-9.
- [22] A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-39.
- [23] European Stroke Prevention Study 2: A study of low-dose acetylsalicylic acid and of high dose dipyridamole in secondary prevention of cerebro-vascular accidents. *Eur J Neurol*. 1995;2(5):416-24.
- [24] The European Stroke Prevention Study (ESPS). Principal end-points. The ESPS Group. *Lancet*. 1987;2(8572):1351-4.
- [25] Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC, et al. Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. *N Engl J Med*. 2021.
- [26] Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, et al. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. *N Engl J Med*. 2020;383(3):207-17.
- [27] Investigators A, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360(20):2066-78.
- [28] Investigators AWGoTA, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367(9526):1903-12.



- [29] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-104.
- [30] Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-17.
- [31] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-92.
- [32] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-91.
- [33] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-51.
- [34] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e143.
- [35] Flint AC, Conell C, Ren X, Kamel H, Chan SL, Rao VA, et al. Statin Adherence Is Associated With Reduced Recurrent Stroke Risk in Patients With or Without Atrial Fibrillation. *Stroke*. 2017;48(7):1788-94.
- [36] Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. *N Engl J Med*. 2020;382(1):9.
- [37] Yoshimura S, Uchida K, Daimon T, Takashima R, Kimura K, Morimoto T, et al. Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke: ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient). *Stroke*. 2017;48(11):3057-63.
- [38] Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6(11):961-9.
- [39] Blanco M, Nombela F, Castellanos M, Rodriguez-Yanez M, Garcia-Gil M, Leira R, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. *Neurology*. 2007;69(9):904-10.
- [40] Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-59.
- [41] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372(25):2387-97.
- [42] Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377(9784):2181-92.
- [43] Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive



- lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359(13):1343-56.
- [44] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379(22):2097-107.
- [45] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376(18):1713-22.
- [46] Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet*. 2019;393(10174):877-88.
- [47] Investigators R-. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet*. 2019;393(10175):1009-20.
- [48] Investigators ET. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet*. 2015;385(9968):617-28.
- [49] Oh MS, Yu KH, Hong KS, Kang DW, Park JM, Bae HJ, et al. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. *Int J Stroke*. 2015;10(5):745-51.
- [50] He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA*. 2014;311(5):479-89.
- [51] Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377(9767):741-50.
- [52] Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol*. 2010;9(8):767-75.
- [53] Bath PM, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, et al. Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: a PROFESS subgroup analysis. *Stroke*. 2009;40(11):3541-6.
- [54] Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8(1):48-56.
- [55] Eveson DJ, Robinson TG, Potter JF. Lisinopril for the treatment of hypertension within the first 24 hours of acute ischemic stroke and follow-up. *Am J Hypertens*. 2007;20(3):270-7.
- [56] Schrader J, Luders S, Kulschewski A, Berger J, Zidek W, Treib J, et al. The ACCESS Study: evaluation of Acute Candesartan Cilxetil Therapy in Stroke Survivors. *Stroke*. 2003;34(7):1699-703.
- [57] Horn J, de Haan RJ, Vermeulen M, Limburg M. Very Early Nimodipine Use in Stroke

- (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke*. 2001;32(2):461-5.
- [58] Kaste M, Fogelholm R, Erila T, Palomaki H, Murros K, Rissanen A, et al. A randomized, double-blind, placebo-controlled trial of nimodipine in acute ischemic hemispheric stroke. *Stroke*. 1994;25(7):1348-53.
- [59] Kitagawa K, Yamamoto Y, Arima H, Maeda T, Sunami N, Kanzawa T, et al. Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis. *JAMA Neurol*. 2019;76(11):1309-18.
- [60] Bath PM, Scutt P, Blackburn DJ, Ankolekar S, Krishnan K, Ballard C, et al. Intensive versus Guideline Blood Pressure and Lipid Lowering in Patients with Previous Stroke: Main Results from the Pilot 'Prevention of Decline in Cognition after Stroke Trial' (PODCAST) Randomised Controlled Trial. *PLoS One*. 2017;12(1):e0164608.
- [61] Mant J, McManus RJ, Roalfe A, Fletcher K, Taylor CJ, Martin U, et al. Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke--Blood Pressure) randomised controlled trial. *BMJ*. 2016;352:i708.
- [62] Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373(22):2103-16.
- [63] Group SPSS, Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382(9891):507-15.
- [64] Group AS, Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575-85.
- [65] Group PC. Post-stroke antihypertensive treatment study. A preliminary result. *Chin Med J (Engl)*. 1995;108(9):710-7.
- [66] Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, et al. Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke: The SHINE Randomized Clinical Trial. *JAMA*. 2019;322(4):326-35.
- [67] Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. *Stroke*. 2008;39(2):384-9.
- [68] Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-72.
- [69] Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-59.
- [70] Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6(5):397-406.
- [71] Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, et al. Implementation of evidence-based treatment protocols to manage fever,

hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet*. 2011;378(9804):1699-706.

[72] Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*. 2013;382(9891):516-24.

[73] Sherman DG, Albers GW, Bladin C, Fieschi C, Gabbai AA, Kase CS, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet*. 2007;369(9570):1347-55.

[74] Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.

[75] Gao S, Wang YJ, Xu AD, Li YS, Wang DZ. Chinese ischemic stroke subclassification. *Front Neurol*. 2011;2:6.