Enchanted2

Enhanced Control of Hypertension and Thrombectomy Stroke Study

An investigator initiated and conducted, prospective, multicentre, randomised outcome-blinded study of blood pressure lowering in patients with acute ischaemic stroke with successful recanalization after mechanical thrombectomy

STUDY PROTOCOL

(Version 3.0 – 18 Aug 2020)

Trial registration: ClinicalTrials.gov (NCT04140110)

CONTACT DETAILS

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INVESTIGATOR AGREEMENT

I have read the following protocol:

Protocol Title: Second Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED2)

Version and Date: Version 3.0 – 18 Aug 2020

I have read this protocol and associated procedure manuals and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention and the conduct of the study.

_____

Investigator's Signature Date (Day / Month / Year)

_____

Name of Investigator (Printed)

_____

Name of Institution (Printed)

Principal Investigator

Co-Principal Investigator Professor Jianmin Liu Changhai Hospital, China	*18 Aug 2020* *Date*	 *Signature*
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1. CONTENTS

2. ADMINISTRATIVE INFORMATION

Protocol History

Version Number	Version Date	Summary of Revisions Made:
1.0	23 Aug 2019	Original
1.2	22 Oct 2019	Additional exclusion criteria
2.0	18 Feb 2020	International Coordinating Centre changed from "Heart Health Research Centre" to "The George Institute for Global Health (Australia) Beijing Representative Office"
3.0	18 Aug 2020	Revision of "Table 2 Schedule of evaluations" and adding subgroup analysis on data collection

Trial/Study Registration

The study has been registered with ClinicalTrials.gov (NCT04140110), and Chinese Trial Registry (ChiCTR1900027785).

Funding

This study has received initial funding from a Program Grant of the National Health and Medical Research Council (NHMRC) of Australia (APP1149987), China National Health Commission Stroke Prevention Committee "China Stroke Prevention and Intervention Project" (GN-2020 R0008), and grants from Changhai Hospital (including "National Clinical Key Specialist Construction Project" 2016). This study also receives funding support from Takeda China.

Study Management & Oversight

ENCHANTED2 is an investigator initiated and conducted study managed by TGI, CHINA. The study will be overseen by a committee of international experts in the fields of neurology, neurosurgery, hypertension, cardiovascular disease, epidemiology and clinical trials.

Steering Committee (SC): The SC is responsible for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The SC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. The SC will also include the grant holders and its members are to be confirmed. The SC will be co-chaired by Professor Craig Anderson and Professor Jianmin Liu.

Central Coordinating Centre (CCC): The CCC is based at TGI, CHINA and is supported by project staff. *Responsibilities:* Day-to-day management of the study, data and project management, committee coordination, assistance with ethics committee and regulatory applications, protocol and procedures for training of participating sites, overseeing of initiation visits and activation of participating centres, monitoring of data quality and adherence to protocol, applicable guidelines and regulations, preparation of study data for analysis and publications.

Glossary of Abbreviations and Terms

ACE-I	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AIS	Acute ischemic stroke
ARB	Angiotensin II receptor blocker
AHA/ASA	American Heart Association/American Stroke Association
BP	Blood pressure
CCB	Calcium channel blocker
CCC	Central coordinating centre
CFDA	China Food and Drug Administration
CI	Confidence interval
CRF/eCRF	Case record form/electronic CRF
CSVD	Cerebral small vessel disease
CT	Computerized tomography
CTA/CTP	Computerized tomography angiography/ perfusion
CV	Cardiovascular
DALY	Disability-adjusted-life-years
DAPT	Dual antiplatelet therapy
DSMB	Data and safety monitoring board
DOACs	Direct oral anticoagulants
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
ENCHANTED	Enhanced Control of Hypertension and Thrombolysis Stroke Study
EQ-5D	EuroQoL Group 5-dimension self-report questionnaire
GCP	Good Clinical Practice
GCS	Glasgow coma scale
HOQ	Hospital organization questionnaire
HT	Haemorrhage transformation
HR	Heart rate
HREC	Human research ethics committee
HRQoL	Health-related quality of life
IAC	Imaging adjudication committee
IC	Informed consent
ICH	Intracerebral haemorrhage
ICH-GCP	ICH Guidelines for Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International normalised ratio
IRB	Institutional review board
ITT	Intension to treat
IV	Intravenous
LAA	Large artery atherosclerosis

LVO	Large vessel occlusion
MR CLEAN	Multicentre Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	Magnetic resonance imaging
MRA	Magnetic resonance imaging angiography
MT	Mechanical thrombectomy
mRS	Modified Rankin scale
NB	Note
NHMRC	National Health and Medical Research Council of Australia
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OAC	Oral anticoagulant
OC	Operations committee
OR	Odds ratio
PI	Principal investigator
PIS	Patient information sheet
PROBE	Prospective, randomised, open, blinded end-point assessed
PTAS	Percutaneous transluminal angioplasty and stenting
RCC	Regional coordinating centre
RCTs	Randomised clinical trials
RR	Risk ratio
rt-PA	recombinant tissue plasminogen activator
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic BP
SC	Steering committee
sICH	Symptomatic intracranial haemorrhage
SITS-MOST	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
SIV	Site initiation visit
SOP	Standard operation process
TGI CHINA	The George Institute for Global Health, China Or Beijing representative office, the George Institute for Global Health (Australia)
TICI	Thrombolysis in cerebral infarction
TMF	Trial master file
UAR	Unexpected adverse reaction
VKA	Vitamin K antagonist

3. PROTOCOL SYNOPSIS

Main Sponsors: 1. Changhai Hospital 2. TGI, CHINA	**Trial Registration:** Clinicaltrials.gov (NCT04140110)
Title: Second Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED2)	
Study Duration: 4 years	**Clinical Phase:** III
Objectives: To determine the effectiveness of more intensive blood pressure (BP) lowering target (<120 mmHg) as compared to a higher BP management target (140-180mmHg) on functional outcome in patients who have had successful recanalization with mechanical thrombectomy (MT) for acute ischemic stroke (AIS) due to large vessel occlusion (LVO).	
Number of Planed Participants: 2257 patients to be recruited from 80-100 hospital sites	
Study Design: International, multicentre, prospective, randomised, open, blinded end-point assessed (PROBE) clinical trial, with the main acute treatment trial of different approaches to BP control and two nested substudies evaluating different approaches to secondary prevention, in this high-risk stroke population.	
Inclusion Criteria: *1)* Age ≥18 years; *2)* Diagnosis of AIS with LVO confirmed by brain imaging; *3)* To receive MT <24 hours after AIS onset according to local guidelines; *4)* Successful recanalization (TICI score ≥2b) after MT; *5)* Sustained systolic BP ≥140 mmHg (defined as 2 successive readings <10 mins) within 3 hours after recanalization; *6)* Provide written informed consent (or approved surrogate). **Exclusion Criteria:** Patients will **NOT** be eligible if there is one or more of the following; *1)* Unlikely to potentially benefit from therapy (e.g. advanced dementia) or very high likelihood of death within 24 hours post-MT, judged by responsible treating clinician; *2)* Other medical illness that interferes with outcome assessments and follow-up (e.g. known significant pre-stroke disability (mRS scores 3-5), advance cancer and renal failure); *3)* Definite indication/contraindication to different intensities of BP lowering treatment; *4)* Specific contraindications to any of the BP agents to be used (eg, patients who are hypersensitive (allergic) to any of the ingredients); *5)* Patients with aortic isthmus stenosis and arteriovenous shunt (exception: patients with haemodynamically inactive dialysis shunt); *6)* Women who are lactating; *7)* Currently participating in another trial which would interfere with outcome assessments.	
Outcome Measures *Primary outcome:* functional recovery, defined as a shift (improvement) in scores on the modified Rankin scale (mRS) at 90 days. *Secondary outcomes:* any intracranial haemorrhage (ICH), symptomatic intracerebral haemorrhage (sICH), early neurological deterioration, imaging assessment (e.g. infarct size, edema volume), death, disability, HRQoL, duration of hospitalization, residence; and health service use for calculation of resources and costs.	

Randomisation and intervention Randomisation is via a central internet-based system, stratified by site, recanalization time from onset (<6 vs ≥6 hours), neurological impairment on the National Institutes for Health Stroke Scale at admission (NIHSS <17 vs ≥17), to ensure balance in key prognostic factors.

Intensive BP lowering group: to commence intravenous BP lowering therapy immediately after randomised to intervention group. The BP target is to achieve BP level of <120 mmHg within 1 hour, and maintain this level at least 72 hours (or hospital discharge if earlier).

Control group: the patient allocated to this group will receive a higher BP target strategy to maintain BP level 140-180 mmHg after MT procedure. BP lowering treatment can be given only when BP level >150 mmHg in order to achieve the target of ≥140 mmHg.

Substudies: The patients who have been enrolled in the main study will be randomised into 2 substudies according to separate eligibility criteria. Both are pilot studies imbedded in the main trial is to recruit as many patients to inform the sample size estimates for the further main study.

Timing of anticoagulation

Objective: To determine the effectiveness of early initiation of anticoagulation (at Day 4±2 of stroke onset) compared with late initiation (at Day 12±2) on secondary prevention of vascular events within 90 days in patients with AF-related AIS due to LVO who receive MT. Randomisation (allocation 1:1 ratio) will be done via the same system as the main study and stratified by site and randomisation of BP intervention. Randomised patients will be allocated to either early group of initiating OAC therapy at Day 4±2 day of stroke onset, or late group of initiating OAC therapy at Day 12±2 of stroke onset. Primary outcome: composite of recurrent AIS, sICH, systemic embolism and/or vascular death within 90 days after randomisation.

Duration of dual antiplatelet therapy (DAPT):

Objective: To determine the effectiveness of short duration of DAPT (6 weeks) compared with standard duration (3 months) on recurrence rate within 12 months in patients with AIS due to large artery atherosclerosis (LAA) who receive MT. Randomisation (allocation 1:1 ratio) will be done via the same system as the main study and stratified by site and randomisation of BP intervention. Randomised patients will be allocated to either short duration group of receiving DAPT (aspirin 100 mg and clopidogrel 75 mg per day) for 6 weeks, or standard duration group of receiving DAPT for 3 months. DAPT treatment will be started within 48 hours after randomisation, and maintained by antiplatelet monotherapy (aspirin or clopidogrel) thereafter. Primary outcome is new stroke event (AIS or ICH) over 12 months.

4. BACKGROUND AND RATIONALE

4.1 Overview

This is an investigator initiated and conducted, multicentre, prospective, randomised, open, blinded end-point assessed (PROBE) clinical trial. ENCHANTED2 has the principle aim of determining the effectiveness of more intensive BP lowering management (systolic target <120 mmHg) compared to less intensive BP management range (systolic 140-180 mmHg) in AIS patients with large vessel occlusion (LVO), to improve functional outcomes after achieving successful recanalization from contemporary mechanical thrombectomy (MT) therapy. There are two embedded substudies evaluating different approaches to secondary prevention in this patient group: early versus delayed initiation of anticoagulation in those with associated atrial fibrillation (AF); and short versus conventional duration of dual antiplatelet therapy (DAPT) in those patients with a clear indication for such therapy following MT.

4.2 Background

4.2.1 Stroke Epidemiology

Stroke is a one of the leading causes of death and adult chronic disability around the world.[1] Although the mortality in high-income countries is decreasing with better management and treatments, the burden of stroke in low-income and middle-income countries (LMICs) is still rising.[2] It is currently the second largest contributor to lives lost through disability after ischaemic heart disease globally in developing countries, and it is third largest contributor to death and disability in developed countries (after ischaemic heart disease and low back and neck pain). In 2015, there were 9 million new onset stroke patients, 42 million stroke survivors, and over 100 million disability adjusted life year (DALYs) lost, worldwide.[3]

Stroke incidence in China was greater than in other countries. The current stroke incidence (247/100 000 person-years [95% CI, 211–283]) and mortality rates (115/100 000 person-years) in China appear to be the highest in the world.[4] It has been the leading cause of death in China in recent years,[4, 5] constituting almost one-third of the total number of deaths from stroke worldwide.[3] There are about 2.4 million new strokes and 1.1 million stroke-related deaths annually, with 11.1 million stroke survivors alive at any given time in China.[5]

Most strokes are due to AIS caused by acute occlusion (‘clot’) of an artery leading to immediate reduction in AIS stroke include large-artery atherosclerosis (LAA), cardioembolism (generally due to AF) and small-vessel occlusion (lacunar), most typically classified according to the Trial of Org in Acute Stroke Treatment (TOAST) criteria.[6]

4.2.2 Acute Managements for AIS

Despite the heavy burden of AIS, progress has been slow in established clear evidence of benefit for acute management strategies. For patients with AIS, timely restoration of blood flow is effective in reducing long-term morbidity. Reperfusion therapy with intravenous thrombolysis (alteplase or recombinant tissue plasminogen activator [rt-PA]) and MT, with either a stent retriever or aspiration device, are now accepted standard of care treatments for AIS patients.

Thrombolysis therapy with intravenous rt-PA is the only licenced medical treatment for patients with AIS, on the basis of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) trial published in 1995, in which 624 patients with AIS were treated with placebo or intravenous rt-PA (0.9 mg/kg IV, maximum 90 mg) within 3 hours of symptom onset.[7] Irrespective of age or stroke severity, and despite an increased risk of fatal ICH during the first few days after treatment, rt-PA significantly improves the overall odds of a good stroke outcome when delivered within 4.5 h of stroke onset, with earlier treatment associated with bigger proportional benefits.[8]

However, the global effect of the therapy is relatively limited, largely due to the narrowed time window for rt-PA, and contraindications such as a history of ICH, coagulation abnormalities and recent history of surgery. In addition, intravenous rt-PA is less effective to patients with LVO. Only about one-third patients with the internal-carotid-artery terminus have an early recanalization after receiving intravenous rt-PA, while other patients will generally have a poor prognosis.[9, 10]

In recent guideline, MT with a stent retriever was recommended after receiving intravenous rt-PA treatment within 4.5 hours of stroke onset, based on the results from five randomised controlled trials (RCTs: Multicentre Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE], Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME], Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial [EXTEND-IA] and Randomised Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset [REVASCAT]), which were carried out from 2010 to 2015 to evaluate the effects of endovascular treatment with primarily stent retrievers plus standard care in AIS patients.[11-15] The following two trials DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE 3 (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) further extended the time window for MT with careful imaging selection.[16, 17] Furthermore, the results of COMPASS (A comparison of direct aspiration versus stent retriever as a first approach) trial demonstrated that compared with stent retriever, direct aspiration had a non-inferior functional outcome, with a shorter recanalization time.[18] However, either intravenous rt-PA or MT has many utility limits with strict onset-to-treatment time, high request to hospital facility and capacity, as well as high cost.

Although strong evidence supporting the use of MT, more evidence regarding on optimizing patient selection with imaging methods,[16, 17] shorten door to puncture time (DPT),[19, 20] and improving perioperative management, especially BP management before, during and after MT is warranted to facilitate the procedure and benefit more patients.

4.2.3 Evidence on BP Control for AIS Patients with MT

Although MT has significantly improved the rate of successful recanalization for patients with LVO, there is still a large proportion of patients who may have a poor outcome (Table 1). [11-17] Except for recanalization status, one of the most powerful predictors of outcomes, other factors including baseline NIHSS score, time to reperfusion, age, hypertension, glucose levels, history of AF and occlusion site may contribute a lot to the outcomes of AIS patients with LVO in the anterior circulation.[21] Among all the factors, BP control emerges as one of the most important controllable factors, which may promote a better outcome if good management has been implemented. However, the evidence on the optimal BP targets after MT, especially for those with successful reperfusion still remains undetermined.

The optimal management of BP in AIS patients remains controversial

The American Heart Association/American Stroke Association (AHA/ASA) guidelines 2018 recommend maintaining BP ≤180/105 mmHg during and for 24 hours after the reperfusion therapy, and < 180/105 mmHg if with successful reperfusion for AIS patients who undergo MT.[22] However, these recommendations are mainly based on the evidence of intravenous rt-PA, as there very limited data to guide BP therapy before, during and after MT.

In particular, clinicians are confused over optimal BP management post-MT, especially for patients with successful recanalization, with variable opinions being expressed. Some recommend a level of 140-160 mmHg, while others insist on normalising systolic BP levels in the range 120-140 mmHg, and a minority consider maintaining high systolic BP around 180 mmHg may enhance collateral blood flow.[23, 24] A US survey of 58 institutions[25] indicate that BP varies according to the success of reperfusion: for those with unsuccessful reperfusion, most institutions accept a systolic BP value ≤180 mmHg; whereas in patients with successful reperfusion there was inconsistency among institutions with 36% (n = 21) using a target systolic BP 120-139 mmHg, 21% (n = 12) 140-159 mmHg, and 28% (n = 16) any value ≤180 mmHg.

Table 1 Recanalization-outcome mismatch in RCTs

Trials	TICI 2b/3	90d mRS 0-2
MR CLEAN [11]	75.4%	32.6%
ESCAPE [12]	72.4%	53%
REVASCAT [13]	65.7%	43.7%
SWIFT PRIME [14]	88%	60.2%
EXTEND IA [15]	86%	71%
DAWN [16]	84%	49%
DEFUSE3[17]	76%	45%

Evidence on BP lowering after MT

Some evidence indicated that higher BP levels were associated with poorer collateral status, worse recanalization results and adverse outcomes in patients with MT treatment.[21, 26] However, evidence on BP lowering and the optimal target after MT has not been established.

Muilder et al. did a post-hoc analysis of the MR CLEAN trial, and confirmed a U-shaped association between baseline systolic BP and functional outcome, with both low and high baseline levels associated with poor outcome such that the optimum outcome nadir was around 120 mmHg.[27] A prospective cohort study consecutively enrolled a total of 217 AIS patients with LVO, who had complete reperfusion after MT to evaluate the association between BP levels and the early outcome.[28] The patients were stratified into 3 groups based on their post-MT BP levels (intensive <140/90 mmHg, moderate <160/90 mmHg and permissive hypertension <220/110 mmHg, or <180/105 mmHg for patients with intravenous thrombolysis). The results showed that high maximum systolic BP levels following MT were independently associated with increased likelihood of 3-month mortality and adverse functional outcome. Martins et al. conducted a retrospective cohort study in 674 AIS patients with acute reperfusion therapy (intravenous thrombolysis or intra-arterial therapies), and also identified a J-shaped association of BP in the first 24 hours and functional outcomes in those who failed recanalization, and a continuous association in those with complete recanalization.[29] Finally, Goyal et al. found that wide BP excursions from mean level during the first 24 hours after MT were associated with poor prognosis.[30]

However, the evidence based on all these studies is complicated by post-hoc bias, chance and confounding errors. Randomised clinical trials (RCTs) are warranted to reliably determine the optimal target of BP for informed recommendation in MT AIS patients.

Intensive BP lowering after reperfusion therapy for AIS patients appears safe

Most AIS patients achieve successful recanalization after MT, with effective restoration of blood flow and less clinical concerns over sICH and other complications. High BP may cause brain injury through promotion of secondary edema and ICH from enhanced reperfusion in ischaemic tissue. Conversely, with impaired cerebral autoregulation in the context of AIS, intensive BP lowering may aggravate cerebral ischemia. Theoretically, the benefits may out way the risks of intensive BP control in patients with complete reperfusion post-MT.

The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), was an international, randomised, open-label, blinded-endpoint, phase 3 trial that assessed the effects of intensive versus guideline-recommend BP lowering in thrombolysis-treated AIS.[31] Among a total of 2196 rt-PA eligible AIS patients with AIS, 1081 were allocated to the intensive group (target systolic BP 130–140 mmHg within 1 hour and 1115 to guideline group (target <180 mmHg) between 2012 and 2018. The mean systolic BP over 24 hours was 144 and 150 mmHg in the intensive and guideline groups, respectively (P <0.0001). Although there with no improvement in the primary outcome of functional recovery, the results showed a reduction in ICH (odds ratio [OR] 0.75; 95% confidence interval [95% CI] 0.60-0.94; P = 0.0137), and no harms from intensive BP lowering within these ranges.[31]

Intensive BP lowering may reduce the risk of sICH after MT

Other studies have shown a reduced risk of sICH with lower systolic BP post-MT. Post-hoc analysis of MR CLEAN trial showed that higher systolic BP was associated with an increased risk of sICH (adjusted OR 1.25, 95% CI 1.09-1.44 per 10 mmHg increase).[27] A retrospective cohort study of Martins et al. showed that systolic BP was an independent predictor of sICH (OR 1.032, 95% CI 1.014-1.049; P < 0.001),[29] while another study showed that higher systolic BP over 24 hours post-MT were associated the more severe haemorrhage within 48 hours and worse 90-day functional outcome.[32]

Rationale for intensive BP control in AIS after successful recanalization post-MT

As from the evidence above, different reperfusion status may have different BP patterns. A line correlation between post-MT BP and outcomes may exist for patients who had successful recanalization post-MT. In addition, intensive BP lowering is safe and may potentially reduce the risk of ICH for patients with reperfusion therapy.

Despite the neutral overall clinical effect seen in the ENCHANTED trial, intensive BP lowering after reperfusion therapy was safe and provided a strong signal for reduced harms associated from ICH/sICH. There were far too few MT patients included in ENCHANTED to make any sensible recommendations over the optimal BP management in this important clinical group. Thus, the hypotheses for testing in the ENCHANTED2 study is that intensive BP lowering post-MT recanalized AIS patients leads to improved functional status with reduced ICH and no other harms.

4.3 Summary

Although MT provides effective recanalization for AIS patients with LVO, many patients survive with residual disability which appears related to systolic BP levels. There is considerable variation in the BP management for this important and increasingly large patient group where current guidelines are based on extrapolating data from those who have received thrombolysis treatment.[7] A definitive randomised trial is required to guide clinical practice, worldwide. Reliable evidence is now required to guide the BP management for post-MT AIS patients who continue to have severe and devastating outcomes. This research program aims to (i) determine the balance of potential benefits and risks of intensive BP lowering to improve

outcomes for AIS patients with successful recanalization after MT (TICI ≥2b), and (ii) provide preliminary data to inform antithrombotic therapy in two nested additional randomised trials.

5. AIMS AND OBJECTIVES

5.1 Primary aim

To test that compared with a higher systolic BP management strategy (140-180 mmHg), intensive BP lowering (systolic target <120 mmHg) after achieving successful recanalization from MT is *superior* on functional outcome (shift mRS) in scores on the modified Rankin scale (mRS) at 90 days in LVO patients with AIS (i.e. corresponding null hypothesis is that there is no difference in 90 day functional outcome between treatment groups).

5.2 Secondary aims

Compared with a higher systolic BP management target (140-180 mmHg), intensive BP lowering (systolic target <120 mmHg) after successful recanalization with MT leads to reduced risk of: any ICH; sICH; early improvement in neurological recovery as measured by NIHSS at 7 days; imaging measurements of infarct size at 24-48 hours; death or major disability (mRS 3-6); separately on death and disability (mRS 3-5); health-related quality of life (HRQoL) using EQ-5D; duration of hospitalisation; residence; and hospital service cost.

6. METHODS

6.1 Design

ENCHANTED2 is an international, multicentre, prospective, randomised controlled, open label, blinded outcome assessment (PROBE) clinical trials involving 2257 AIS patients with LVO to be recruited from 80-100 hospitals in China, and up to 50 hospitals in other countries dependent on funding. Consent will be obtained upon the patient's presentation to hospital and before undergoing the cerebral angiography, but randomisation will be undertaken post-MT according to eligibility criteria. Randomised allocation (1:1 ratio) of intervention will be done in a, using a central, automated, mobile APP-based randomisation software according to minimized method stratified by hospital, time from onset to recanalization (<6 vs ≥6 hours), NIHSS scores at admission (<17 vs ≥17). All required data will be collected by investigators and entered into internet-based electronic data capture (EDC) system. Endpoint assessment will be undertaken by experts blind to treatment allocation. The study design is summarised in Figure 1.

6.2 Study Population

All AIS patients presenting to participating centres with LVO confirmed by brain imaging, who meet standard criteria for MT therapy according to local guidelines will be considered for the trial. Primary responsibility for recruitment of patients will lie with each site Principle Investigator (PI). It is anticipated that successful recruitment will require the active involvement and disciplinary cooperation of stroke team staff, including emergency department, neurologists, interventionists and anaesthetists, since rapid referral and treatment of patients early after symptom onset and successful recanalization after receiving MT therapy is required. Rate limiting steps after presentation are anticipated to include:

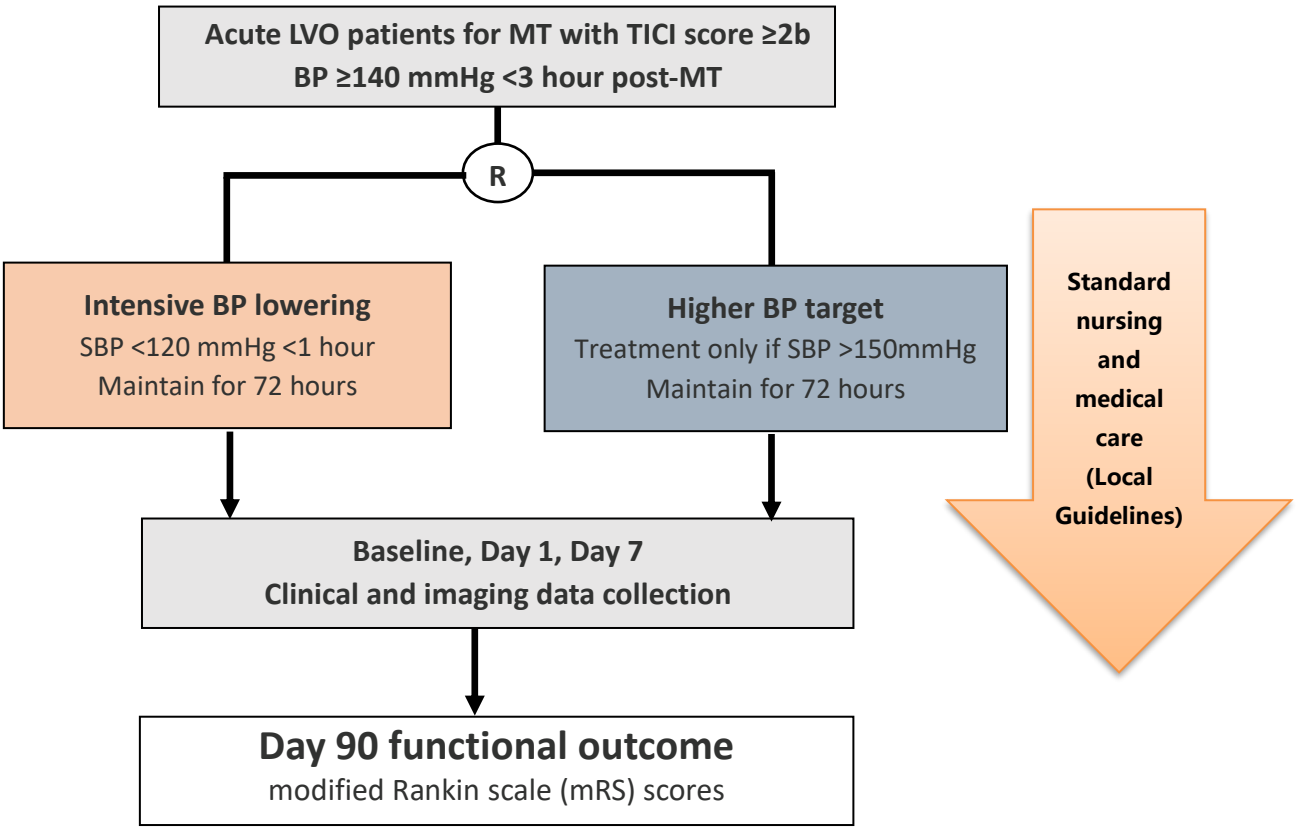
1) completion of brain imaging
2) receipt of informed consent
3) assessment at admission and completion of MT-related procedures
4) assessment of patients eligible to receive intensive BP lowering treatment after obtaining achieving recanalization via MT therapy

5) administration of randomised treatments

In order to facilitate recruitment, study centres should try to obtain consent from the patient or guardian before the MT procedure, and to confirm/determine a patient's eligibility as early as possible within 3 hours after the LVO is successfully re-canalized according to TICI score, and with the goal of the randomisation-to-treatment time being 15 minutes.

All devices for MT approved by China Food and Drug Administration (CFDA) for this purpose, are allowed in the trial as a first line of devices. Other mechanical devices are allowed as a second option, when the first device has failed according to the interventionist, usually after 3 passes (**Appendix 2**). The further choice of the particular device for a certain patient is left to the discretion of the interventionist.

Figure 1. Study schema



6.3 Inclusion / exclusion criteria

*To be eligible for inclusion for this study, patients **ARE** to satisfy all of the following criteria:*

1) Adult (age ≥18 years)
2) Clinical diagnosis of AIS with LVO (anterior or posterior circulation) on imaging
3) To receive MT <24 hours after AIS onset according to local guidelines
4) Successful recanalization (TICI score ≥2b)
5) Sustained systolic BP ≥140 mmHg (defined as 2 successive readings <10 minutes) within 3 hours after recanalization
6) Provide informed consent (or by appropriate proxy, according to local requirements)

*Patients will **NOT** be eligible if there is one or more of the following:*

1) Considered unlikely to benefit from therapy (e.g. advanced dementia, major pre-stroke disability, high likelihood of death within 24 hours post-MT on the basis of clinical assessment), as judged by the responsible treating clinician
2) Other medical illness that interferes with outcome assessments and follow-up (e.g. known significant pre-stroke disability (mRS scores 3-5), advance cancer and renal failure)
3) Definite indication/contraindication to either immediate intensive BP lowering (SBP <120 mmHg) or a higher BP target (SBP 140-180 mmHg)
4) Specific contraindications to any of the BP agents to be used (eg, patients who are hypersensitive (allergic) to any of the ingredients)
5) Patients with aortic isthmus stenosis and arteriovenous shunt (exception: patients with haemodynamically inactive dialysis shunt)
6) Women who are lactating
7) Currently participating in another trial which may interfere with outcome assessments

All AIS patients screened for the study that are not included, as well as recruited patients, must be recorded on a screening/enrolment log. This information is to be uploaded to the CCC database. The decision of eligibility is on the attending clinician's interpretation and consideration for the balance of potential benefits and risks pertaining to the level of BP control on each particular patient.

6.4 Ethical Issues

This study will be conducted in compliance with the principles outlined in the World Medical Association's Declaration of Helsinki **(see Appendix 5)**.

6.4.1 Institutional ethics committee approval

Each participating centre must obtain written approval(s) from their Hospital Human Research Ethics Committee (HREC) (or Institutional Review Board [IRB]), and other regional or national regulatory bodies before patient recruitment can commence. Any protocol amendments, serious adverse event (SAE) reports and routine reporting to the IRB will be the responsibility of the site PI, who has the responsibility of delegating aspects of the study procedures to prospectively approved members of his research staff.

6.4.2 Consent

The majority of patients admitted with AIS require emergency care, and aspects of MT therapy and management of hypertension need to be undertaken urgently. The nature of this acute condition means that the patient may be too unwell to comprehend the information that must be given in the consent process and which needs to be obtained swiftly to avoid delays in urgent treatment. The optional consent procedures for this study are detailed below and should be followed according to local IRB guidelines.

Ideally, the consent to participate in the study is to be undertake prior to MT, and only patients who are eligible post-MT will be randomised into the study.

<u>Patient Consent</u>

Wherever possible, the patient will be approached to directly give written informed consent. An information statement will be given to the patient and the implications for consenting to the study will be explained by a clinician familiar with the study protocol.

Person Responsible Consent

If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient's 'person responsible' will be approached to provide informed consent on his or her behalf.

The patient will be made aware of this process as soon as they are well enough and have an opportunity to withdraw the consent. If willing to continue participation in the study, the patient will be asked to sign their own consent form.

If the patient is dying or is still unable to record their personal consent by the time of completed follow up on the study, the consent given by their person responsible will stand and trial data will be retained. The reason for not obtaining the patient's consent will be documented, dated and signed in the patient's file.

If a patient is discharged from hospital before it has been possible to gain personal consent, the PI will make attempts to inform the patient of the study and gain written consent. The reason for not obtaining the patient's consent will be documented, dated and signed in the patient's file.

Guardianship tribunal consent

In the situation where a patient is unable to give consent and a 'person responsible' is not available or cannot be contacted, clinicians should seek the approval of a guardianship tribunal or other appropriate authority, before enrolling eligible patients into the study. The patient will be made aware of this process as soon as they are well enough and have an opportunity to withdraw the consent. If willing to continue participation in the study, the patient will be asked to sign their own consent form. If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient's 'person responsible' will be approached as soon as possible to provide informed consent on his or her behalf.

In the case of a patient's death, the PI should use discretion on a case by case basis before contacting the 'person responsible' in recognition of the potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient or surrogate consent will be document in the patient's file.

Delayed consent

The circumstances surrounding emergency care research are such that it may not always be possible to obtain consent from either the patient or next of kin without delaying the initiation of treatment, and therefore risk reducing any potential benefits to the patient. In the situation where a patient is unable to give consent and a next of kin or other person responsible is not available or cannot be contacted, clinicians may enrol eligible patients and inform the patient or their person responsible for the patient as soon as possible so that delayed consent can be requested. The reasons for being unable to obtain prior consent will be documented, dated and signed in the patient's file.

If the patient should die or continue to be unable to give informed consent at the end of the trial follow up period, the next of kin or person responsible should be approached to obtain delayed written consent. In the case of a patient's death, the PI should use discretion on a case by case basis before contacting the next of kin or surrogate, in recognition of the

potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient or person responsible consent will be document in the patient's file.

Delayed consent in a clinical trial of emergency care is considered by the World Medical Association in the Declaration of Helsinki. This document states:

> "*Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population*."

This study includes such potentially eligible patients.

The Australian National Health and Medical Research Council (NHMRC) also give guidance to human research ethics committees on this issue:

> "*When the nature of the research procedure is such that conformity to the principle of consent is not feasible, and neither the individual nor the individual's representative can consider the proposal and give consent in advance, a HREC may approve a research project without prior consent provided it is satisfied that:*
>
> *(a) inclusion in the research project is not contrary to the interests of the patient; and*
>
> *(b) the research is intended to be therapeutic and the research intervention poses no more of a risk than that which is inherent in the patient's condition and alternative methods of treatment; and*
>
> *(c) the research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care; and*
>
> *(d) as soon as reasonably possible, the patient and/or the patient's relatives or legal representatives will be informed of the patient's inclusion in the research and of the option to withdraw from the research without any reduction in quality of care".*

All four criteria apply to this study protocol including the uncertainty about BP management after MT in the medical profession and the current guidelines.

Withdrawal of Consent

The information statement provided to the patient and/or the next of kin or surrogate will clearly state that the patient can be withdrawn from the study at any time without prejudice and explanation. Such withdrawal should be documented in the patient's file. If withdrawal of consent relates to the BP management alone, data collection can continue on documentation of this fact in the patient's files.

6.4.3 Confidentiality and Privacy

Every precaution should be taken to respect the privacy of patients in the conduct of the study. Only de-identified data will be submitted to the CCC at TGI, CHINA to maintain patient confidentiality. However, in the course of monitoring data quality and adherence to the study protocol, the study monitor will refer to medical records at the participating hospital. This information will be included in the PISCF.

6.5 Site selection

Site eligibility criteria: To participate, sites are required to fulfil certain eligibility criteria:

1) Have an established acute stroke service (i.e. in an acute stroke unit, neurosurgical unit, neurology unit), defined by (i) having staff organised as part of a coordinated multidisciplinary team; (ii) having staff with some knowledge and skills in the stroke management; (iii) have staff interested and capable of participating in research;
2) At least 50 cases of MT per year;
3) Multimodal imaging (CT angiography (CTA) / CT perfusion (CTP) and/or MRI) is available;
4) Obtain necessary HREC and other relevant approvals from hospital management;
5) Agree to enter data via the internet to a secure server built and based on the Taimei, Alibaba cloud, in China;
6) Nominate key research staff assigned to the project to obtain consent from participants;
7) Comply with the requirements of good clinical practice (GCP/ICH-GCP);
8) Agree to the following conditions:
   - adhere to the protocol
   - collect data on patients' stay in hospital
   - record any SAEs noted during the 3 months of follow-up of patients
   - Sign a contract agreement before the commencement of recruitment.

Responsibilities of the regional leader are:

1) work with hospitals to ensure investigators comply with the protocol in a seamless way;
2) provide regular training for MT and oversee the operation procedures after patient enrolment;
3) liaise with the CCC staff on issues of site eligibility.

Responsibilities of the site PI are:

1) ensure all sub-investigators, nursing staff and coordinators, undertake the necessary pre-study training programs regarding the protocol and positioning of the patients;
2) agree to comply with GCP/ICH-GCP requirements;
3) submit and obtain EC approval and ensure compliance to EC requirements;
4) receive training on the protocol, and to 'champion' the study at the hospital;
5) provide refresher training for existing and new staff on the intervention on a regular basis;
6) conduct spot checks adherence to the randomised intervention;
7) assist in problem-solving and propose solutions to resolve any local issue that may pose a barrier to the adherence to the intervention;
8) oversee the data collection;
9) conduct spot checks of the patient screening and enrolment log (Form A);
10) record and report all SAEs during 3 months' follow-up period.

In the selection of suitable sites, there is a healthcare organization questionnaire (HOQ), provided by local leader to collect preliminary information about the site, so the CCC can ascertain the suitability of the site to participate in the study.

Hospital organisational questionnaire (HOQ): To assist the implementation of the intervention in each site, it is important to know the organisational structure of the site and the various areas within the site that will be involved in the intervention. Therefore, each site will have to complete a HOQ to assist the CCC prepare the training and site initiation visit.

6.6 Randomisation

After confirmation of eligibility within 3 hours post-MT, patients will be randomised via a central mobile APP-based, password protected randomisation system developed by Taimei, China. This will be done by connecting the study centre (e.g. catheter lab or stroke unit) to the server at Ali Cloud where the patient will be registered and the randomised treatments will be assigned for each particular patient.

The randomisation sequence will use a minimisation algorithm to ensure balance in key prognostic factors. Patients will be stratified according to:

1) Site of recruitment
2) Time from onset to recanalization (<6 vs ≥6 hours)
3) NIHSS score at admission (<17 vs ≥17)

6.7 Treatments Allocation

Attending clinicians are required to consider their level of clinical uncertainty over the balance of potential benefits and risks pertaining to the level of BP control in each particular patient. Investigators are encouraged to adhere to study protocols, provide active care, but are free to modify a patient's treatment as required according to clinical judgment.

Intensive BP lowering group

The aim is to achieve a systolic BP level of <120mmHg within 1 hour after randomisation and to maintain this BP level for the next 72 hours (or until hospital discharge or death if this should occur earlier). A standardised intravenous (i.v.) BP lowering regimen using locally available and approved i.v. BP lowering agents will be used, commenced immediately after randomisation in either the catheter lab or a high dependency area (e.g. acute stroke or neurointensive care unit) as is usual for patients receiving MT.

BP lowering will be titrated by repeat i.v. bolus or infusion, with a systolic BP of 100 mmHg being the safety threshold for cessation of therapy. It is anticipated that i.v. agents will be required for at least the first several hours in most cases but the timing of switch to oral BP lowering agents will be at the discretion of the responsible clinician according to BP control and patient status. It is also expected that i.v. therapy will continue to be required during the initiation of oral antihypertensive therapy, to maintain the systolic BP levels 100-120 mmHg.

When administering BP lowering treatment, care is required to ensure that severe hypotension is avoided in patients by checking first for potential dehydration and providing intravenous fluids.

Since the study seeks to address the impact of BP lowering and not a specific agent, and to ensure the trial result is maximally generalizable to existing routine practice, some flexibility is allowed in the use of locally available i.v. agents (e.g. urapidil, hydralazine, metoprolol, clevidipine), but all other aspects treatment are standardized across sites. Patients on prior oral BP lowering agents should have this continued if possible and antihypertensive therapy prescribed when patients are clinically stable as per guidelines for secondary stroke prevention. Investigators are encouraged to adhere to study protocols, provide active care, but are free to modify a patient's treatment as required according to clinical judgment.

I.v. treatment protocol

I.v. treatment protocols, based on available medications, are provided in Appendixes 1A to 1F. The i.v. treatment will be titrated against regular BP monitoring to achieve a target systolic BP range (100-120 mmHg) within 3 hours after successful reperfusion with MT. It is anticipated that i.v. control of systolic BP will be required for at least several hours.

Oral treatment protocol

The switch from i.v. to oral BP lowering treatment will be made at the discretion of the responsible physician, depending upon the control and stability of the BP and the clinical status of the patient. It is anticipated that oral treatment will be started by 24 hours.

The oral treatment protocol will also include a defined strategy for titration of treatment to achieve effective early systolic BP control once oral treatment is commenced. If the patient is unable to swallow, treatment should be administered via nasogastric tube.

For the intervention group, the goal is to maintain systolic BP levels <120 mmHg for at least 72 hours of hospital stay. If the patient is transferred to another hospital facility within 72 hours, then attempts should be made to continue therapy to achieve the systolic BP target of <120mmHg. The target systolic BP after hospital discharge remains 130/140 mmHg, as guideline-based recommendations for second stroke prevention. BP levels will be reviewed at 90 days follow-up and medication adjusted as necessary to maintain systolic BP <130/140 mmHg as per contemporary guidelines.

Control group (higher BP target)

Patients allocated to the control group will receive management of BP to maintain systolic BP 140-180mmHg. Appendix 1G outlines the protocol for control patients. For this group, the attending clinician should stop BP lowering treatment if the systolic BP is ≤150 mmHg in order to maintain a higher BP target level of 140-180 mmHg comparing to intensive group. The oral and i.v. agents used will be the same as in the intensive BP lowering group as detailed in Appendixes 1A to 1G. Oral antihypertensive therapy may be started at any time the treating physician feels the patient is stable. Oral therapy must be started by Day 7. The target systolic BP after hospital discharge is <130/140 mmHg, as per contemporary guideline-based recommendations for high risk cardiovascular disease patients.

Discontinuation of allocated management

The investigator must not deviate from the protocol except the patient/surrogate chooses to withdraw consent to participation in the study. However, allocated management in either group should be discontinued or modified if any of the following occur:

a. SAEs, which are in the opinion of the investigator, related to the trial protocol (refer to appropriate section for definitions).

b. The investigator feels it is in the subject's best interest.

Follow-up data will be collected for all treated subjects except those who specifically withdraw consent for release of such information.

6.8. Study Outcomes

Primary outcome

Functional outcomes defined as a shift (improvement) in scores on the mRS at 90 days (3 months). The mRS is a widely used instrument for grading the impact of stroke treatments, with scaling of: 0 = no symptoms at all; 1 = no significant disability despite symptoms, but able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all

previous activities but able to look after own affairs without assistance; 3 = moderate disability requiring some help, but able to walk without assistance; 4 = moderate-severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability, bedridden incontinent, and requiring constant nursing care and attention; 6 = dead.

Secondary outcomes are:

1) ICH: a) sICH, based on National Institutes of Neurological Diseases and Stroke (NINDS) criteria of brain imaging (or necropsy) confirmed ICH with ≥ 1 points deterioration in NIHSS score or death within 36 hours from baseline; b) sICH, defined by Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria, as large ('type II') parenchymal ICH with ≥ 4 points decline in NIHSS score or death within 36 hours from baseline; c) sICH, defined by the new Heidelberg Bleeding Classification (HBC) criteria; d) ICH of any type in brain imaging ≤ 7 days of treatment; e) any symptomatic ICH (sICH) after MT within 90 days. ICH will be assessed by CT imaging and adjudicated centrally.[33]

2) Imaging endpoints: a) infarct size growth assessed by MRI at 48 hours; b) edema volume assessed by CT at Day 7.

3) Death or dependency measured by NIHSS at 7 days;

4) The followings at 90 days: Death or major disability (mRS 3-6); separately on death and disability (mRS 3-5); health-related quality of life (HRQoL) using EQ-5D; duration of hospitalisation; residence and hospital service cost.

6.9 Economic Evaluation

Economic evaluation provides value judgement for health policy makers when they consider to scale-up the health intervention. In ENCHANTED2 trial, the intervention of BP lowering will be initiated after successful recanalization and the BP target will be maintained for at least 3 days (or hospital discharge if earlier). Since an increasing number of patients receive MT annually, it is important to know whether the ENCHANTED2 is cost effective compared to the conventional care. A within-trial economic evaluated will be conducted to compare the incremental costs including costs of intervention and difference in health service cost versus the incremental effectiveness which is expressed using quality-adjusted life years (QALYs). The (trial-based) incremental cost effectiveness ratio will be calculated and then compared to the willingness-to-pay threshold in China and other countries to determine the cost-effectiveness of ENCHANTED2. The economic evaluation will be conducted from the healthcare payer's perspective.

6.10 Data Collection and Follow-up

Registration, baseline assessment, and randomisation should be achieved over 15 minutes. Doctor/nursing attendance with the randomised patient is likely to be required for 1-2 hours post-randomisation to ensure the titration of BP lowering in the active group, and consistent BP recordings. All patients are followed daily for 1 week, and then 90 days unless death occurs earlier. Key demographic and clinical data will be collected at randomisation. Follow-up data will be collected on 3 occasions: 24 hours, 7 days (or hospital discharge if sooner), and 90 days. The 90 day evaluations will be conducted in-person or by telephone, by a trained staff member at the local site who is blind to the treatment allocation. Brain imaging (CT scan and/or MRI, with any associated diffusion/perfusion and angiogram images) will be conducted according to standardized techniques at baseline, within 24-48 hours (ie next day follow-up scan), and at a later stage in all surviving patients who may deteriorate or for other clinical

reason during follow-up. Brain imaging (CT scan and/or MRI) must be uploaded to the ENCHANTED2 server, either directly from the hospital site (if they have suitable broadband internet) or via the RCC office, to be analyzed centrally for measurement of any ICH or haemorrhagic complications of the ischemic lesion, and for future measurement of areas of infarction, ischemic penumbra, and site of LVO. The LCC will keep a hard copy in an uncompressed DICOM format onto a CD-ROM for monitor site verification **(see Appendix 3)**. Trial management is facilitated by an established internet-based system.

All randomised patients will be followed up to 90 days, or death if prior to 90 days. Patients who do not follow the protocol and/or discontinue allocated management should still be followed up to 90 days as their data will be analyzed on the 'intention to treat' principle. **Table 3** illustrates the schedule and nature of the data collection required during the study period. The paper version of the case reports forms (CRFs) will be supplied with the procedure manual, as a reference only, together with a guide to completion of each data element and a definition of terms.

All data entry will be completed on a password protected study website. This web-based data management system will allow for real time data query generation for values entered outside of pre-set valid ranges and consistency checking. This system will speed up data reporting and assist overall trial management for all participating centres. In addition to the web-based data entry, BP and drug usage will also be recorded on a paper CRF at the patient's bedside as part of the patient's usual medical record management.

6.10.1 Screening Logs

Each site should keep log of all AIS patients with LVO confirmed by brain imaging arriving <24 hours of symptom onset (or last known well) and who were considered for the study but subsequently excluded. The screening log will record patients' initials and date of admission together with a brief description of the main reason as to why a patient was not randomised. The log will be used by the Research Coordinator, PI and the CCC to monitor recruitment and to identify specific barriers to randomisation of eligible patients. It is also a requirement for the reporting of results of clinical trials.

6.10.2 Patient Contact Details Log

Each centre will keep a record of the contact details and information of next-of-kin for all randomised patients. This will be kept at the participating centre in a locked filing cabinet and in accordance with local policies on the custody of confidential clinical trial data. The Patient Contact Details Log will also be used to document any issues arising from the consent procedure, attempts at follow up and information on protocol violations. The Patient Contact Details Log will be used by the Research Coordinator and PI in managing the consent process, follow-up schedule, and in responding to queries from the CCC.

6.10.3 Randomisation Assessment (Form A)

All AIS patients obtaining successful recanalization after MT will be assessed by the responsible physician for eligibility to the study using a checklist of the eligibility criteria described previously. This form will be kept at the participating site in a locked filling cabinet with the study patient's file.

6.10.4 Baseline Data (Form B)

The following information is to be collected on admission:

- BP, Heart rate (HR) and blood glucose (BG) at admission
- Demography, and medical history

- Medications at time of admission
- Baseline GCS and NIHSS scores
- Initial brain imaging (CT and/or MRI)
- Other imaging (CTA/MRA, CTP/MRP, DSA)
- Management with rt-PA if performed
- Details of MT procedure: anesthesia methods, use of GP IIb/IIIa receptor inhibitors, MT device(s) and their sequence, number of retrieval attempts, door-to-puncture time (DPT), onset to reperfusion time, TICI score after MT, NIHSS score after MT.
- Baseline blood tests and electrocardiogram (ECG)
- Pattern of neurological deficits

6.10.5 Follow up Data

Day 1 (Form C)

The primary goal of assessments within the first 24 hours will be to ensure adherence to the allocated the protocol. BP and administered medication will be recorded. BP will be recorded supine in the non-paretic arm from the automated, electronic device used at the Clinical Centre. BP will be recorded every 15 minutes for the first hour, then hourly for the next 5 hours, and 6 hourly from 6 hours to 24 hours. When i.v. boluses are given, HR and BP should be re-checked and recorded 5 and 15 minutes later. The following information will be recorded.

- BP
- BP lowering medication
- GCS and NIHSS scores at 24 hours
- Follow up brain imaging (CT brain and/or MRI) should be undertaken at 24-48 hours post-MT
- If other imaging investigations are performed (i.e. transcranial Doppler), these should be documented in the CRFs
- Antithrombotic medications
- Follow up blood tests
- Standard stroke care assessment

Day 7 or discharge if earlier (Form D)

On Day 7 or on the day of hospital discharge/transfer or death if prior to Day 7, the contact details of the patient or caregiver should be confirmed to facilitate follow up assessments. The following information will be recorded:

- GCS and NIHSS score
- Dependency assessed with the mRS
- BP
- BP lowering medication (medications used during Days 2 to 7)
- Medications and key specific treatment received during hospitalization
- Other aspects of acute stroke management during hospitalization

- Prognosis prediction from clinicians
- Date of discharge or transfer from hospital
- Repeat brain CT or MRI
- Healthcare costs and details of blood pressure lowering treatment.

BP Monitoring Chart (Form E)

As usual nursing care during the study period, the BP assessments in 7 days will be used to check adherence to BP management protocol.

Day 90 Follow-up (Form F)

These assessments are to be undertaken by an investigator who was not involved in the clinical management of the patient, and blind to the randomised treatment allocation. On 90±7 days, all surviving patients will be evaluated through a telephone interview or at a face-to-face consultation.

Detailed resource utilization data, hospital billing data, physical function and patient reported quality of life data were collected for patients from the time of randomisation through 90-day follow-up. These data were used to calculate direct healthcare costs and QALY during the initial 90-day period based on international and national guidelines.[34, 35]

- BP
- Dependency assessed with the mRS [36]
- HRQoL measured by the EQ-5D [37]
- Patient living status (e.g. home, high care)
- Any complications or hospitalization since going home
- Any medication currently used
- Healthcare related cost.

Death

Patients who have died prior to any of the above scheduled assessments, cause of death documentation will be collected with date and time of death. Copies of post-mortem reports, hospital record entry or death certificate, should be kept with the Patient Contact Details log to assist in trial monitoring by the CCC. An SAE form is to be completed for all deaths during the study period, stating the primary and underlying cause of death.

Withdrawal of allocated management and protocol violations

A form will be provided to record the date and circumstances surrounding any deviation from the protocol or missed assessments.

Consent

Consent will be documented in the patient's progress notes and CRF and the type(s) of consent obtained will also be recorded on the database.

Serious Adverse Events (SAEs)

All SAEs will be recorded on the SAE form, and completed on the electronic CRF or faxed/emailed from a printed form to the CCC within the prescribed time. Additional information may be requested to provide supplementary information on the event and outcome.

Table 2 Schedule of evaluations

Evaluation	Baseline (Prior Randomisation)	Day			
		1	7[a]	90[b]	365[b]
Eligibility	**X**				
Brain imaging (CT ± angiogram or MRI± angiogram or DSA)	**X**	**X**	**X**		
BP	**X** (BP x 2)	**X**** q 15 min 1h 6h	**X** q12h	**X**	
HR	**X**				
ECG	**X**				
Consent	**X**				
Medical history, prior medications	**X**				
Details of rt-PA (if performed) and MT	**X**				
Physical exam GCS/ NIHSS	**X**	**X**	**X**		
Functional assessment with mRS	**X**		**X**	**X**	
HRQoL assessment with EQ-5D				**X**	
Routine blood tests	**X**	**X**			
BP lowering treatment		**X**	**X**	**X**	
Antithrombotic and other medications		**X**	**X**	**X**	
Standard stroke care		**X**	**X**		
Hospitalized or not			**X**	**X**	
Contact details for Follow-up		**X**	**X**		
Hospital service cost			**X**	**X**	
SAEs	**X**[c]	**X**	**X**	**X**	**X**

** At any point where intravenous antihypertensive agents are administered, BP and HR should be recorded 5 and 15 minutes later.

(a) Or the day of discharge if prior to day 7.

(b) Information collected at a face to face consultation or through a telephone interview.

(c) After informed consent.

7. SAFETY

7.1 Data and Safety Monitoring Board (DSMB)

Responsibilities: Monitor efficacy variables and safety outcomes for early dramatic benefits or potential harmful effects and provide reports to the SC on recommendations to continue or temporarily halt recruitment to the study. The DSMB will be governed by a charter that will outline their responsibilities, procedures and confidentiality. They will review unblinded data from the study at regular intervals during follow-up and monitor BP differences between the two groups, drop-out, and event rates. The first meeting will be held within 3-6 months after the start of the study recruitment. Two formal interim analyses will be planned to review data relating to treatment efficacy, participant safety and quality of trial conduct. Prior to the first interim analysis a detailed plan will be developed to:

- Describe the methodology to be used in the statistical analyses.
- Specify rules if the study is to be halted.
- Specify rules on data handling conventions used to perform the analyses.
- Describe the procedure to be used to account for missing data.
- Outline interim analysis.

7.2 SAEs

7.2.1 Definitions

The mechanisms for reporting and notifying SAE are based on the guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP). As defined by the WHO International Drug Monitoring Centre (1994):

A SAE is any untoward medical occurrence that:

- results in death
- is life threatening in the opinion of the attending clinician (ie the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect (Note that the females in the study population are likely to be post-menopausal)
- is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above

7.2.2 Recording and Reporting

A SAE form must be used to record the details of the event and this will include a full description of the event, classification of the event using the above definitions, the PI"s opinion on the causal relationship to the randomised management group and the timing of the event. All SAEs

should be reported to the CCC within 24 hours or as soon as the event is recognised. The PI will be required to submit a follow up report to provide further information so that the outcome of the SAE can also be recorded. The PI is responsible for reporting the SAE to the IRB according to local guidelines.

7.2.3 Monitoring of SAEs

The CCC will closely monitor all SAEs for any relationship to the study procedures and protocol and clustering of events at a particular site. The protocol will be amended or the study will be stopped earlier if an excess of particular SAEs appear to be protocol related, for example severe hypotensive events requiring emergency treatment in the intensive BP lowering group. In addition, the CCC will submit all SAEs to the independent Data Safety Monitoring Board (DSMB) for review outside of the planned interim analysis meetings.

8. QUALITY ASSURANCE

The study will be conducted at sites which successfully pass the site selection process, in accordance with the principles of the ICH-GCP and all relevant local, national and international guidelines and regulations. RCCs will be set-up in the various regions to facilitate the compliance of the protocol to local requirements. The RCCs will receive training and assistance to set-up documentation required for the study from the CCC. There will be regular meetings/teleconference between the RCC and CCC staff. Manuals and Guidance will be developed by the CCC in liaison with the Operations committee (OC).

8.1 Monitoring of Participating Centres/Sites

Prior to the initiation of the study at any participating centre, all designated research staff including the PI, Co-Investigator(s) and Research Nurse(s) will attend a training meeting on the study procedures. A study monitor, appointed by the CCC, will visit each participating centre to confirm there are adequate facilities and medical resources to conduct the study. In addition, all Investigators will be provided with materials detailing all study procedures. Before initiating the study, the PI and any Co-Investigators will provide up-to-date curriculum vitae (CV) in English to the CCC. The CVs of other designated research staff at the participating centre will be collected during the course of the study.

During the study, representatives of the CCC will visit all participating centres a minimum of twice in the recruitment phase of the study. The purpose of these visits will be to ensure that the study is conducted according to the protocol, ICH-GCP guidelines and meets relevant regional regulatory requirements. The monitor will verify relevant source documents according to a detailed monitoring plan available as a separate document.

A report of each visit will be prepared by the monitor and reviewed by the CCC.

In summary, the specific aims of the monitoring program will be to:

- confirm the existence of each patient
- confirm that the consent procedure has been documented
- confirm the eligibility of each patient
- review source documents for 100% of the SAEs and primary outcomes
- review 100% of source data from 10% of randomly selected patients at each centre

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation (for 5 years).

8.2 Auditing and Inspection by Government Regulatory Authorities

In addition, the study may also be audited by the third party and inspected by inspectors appointed by government regulatory authorities. CRFs, source documents and other study files must be accessible at all study sites at the time of auditing and inspection during the course of the study and after the completion of the study.

9. DATA MANAGEMENT

The internet based data management system is managed at Taimei, which has extensive experience in clinical trial data capture and security. Registration and data entry will be performed at the participating sites via the password protected, via the encrypted HTTPS connection. Only staff listed in the delegation log will be given unique individual password to access the internet-based data management system.

This system, developed by Taimei for data capturing and the data variables will have logic checks within the acceptable ranges and mandatory fields to ensure accuracy and reduce missing data. Reports and data query management will also be included in the system to assist with centralised online monitoring by the CCC and the RCC.

Paper CRFs will be provided for sites preferring to use these for the initial collection of data. These forms will be used as source document and will need to be signed and dated by the investigator completing the form.

All computerized forms will be electronically signed (by use of the unique password) by the authorised study staff and all changes made following the initial entry will have an electronic dated audit trail. It is the requirement that the collection of data and transfer of information for the 90 day follow-up assessment has to be approved by the local IRB for each site.

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size

The study is designed with 90% power to detect an odds ratio (OR) of 0.77 at 90 days between the randomised groups in AIS patients with successful post-MT reperfusion using an ordinal logistic regression. Assuming a distribution of mRS in control group is 10.0%, 16.9%, 19.1%, 16.9%, 15.6%, 6.2%, and 15.3% for scores of 0 to 6, respectively, corresponding to a 6.48% absolute decrease in the proportion of patients experiencing a bad outcome (mRS of 3-6), from 54% down to 47.52%, according to the results of the meta-analysis made by HERMES collaboration.[38] This also translates to a 12% relative risk reduction (relative risk of 0.88). The sample size is 2257 subjects to demonstrate this treatment effect with 90% power and 4.82% type-1 error which we used the Haybittle-Peto boundaries taking into account 2 interim analyse during the study period. The sample size allows for 5% lost to follow-up and 5% drop-in/drop-out.

10.2 Statistical Analyses

The intention to treat (ITT) principle will be applied in analyzes. Baseline characteristics will be summarised by treatment group. The primary end-point will be analyzed by means of an ordinal logistic regression with adjustment for stratification variables. Sensitivity analyses including additional covariate adjustments and different assumptions about the missing data mechanism will be conducted to assess the robustness of the results. Continuous endpoints, such as blood pressure will be analysed using a repeated-measure linear mixed model adjusted for the stratification factors. The number of patients reporting any SAE, the occurrence of specific SAEs, and discontinuation due to SAEs, will be tabulated using MedDRA terminology.

Heterogeneity of treatment on the primary endpoint and sICH will be assessed in subgroups: age (<65 vs ≥65 years), onset time to recanalization (<6 vs ≥6 hours), systolic and diastolic BP (above vs below median), ethnicity, presumed etiological AIS subtype, NIHSS at baseline (above vs below median), ASPECT score (<6 vs ≥6) in the intensive BP lowering group, whether the patients enrolled after 6 hours meet DEFUSE 3 perfusion imaging criteria late window thrombectomy (ASPECT score and perfusion imaging criteria will be assessed by RAPID software, which will be installed at the sites by iSchemaView, Inc.).

Details of all analyses will be specified a priori in a full Statistical Analysis Plan (SAP).

We anticipate conducting 2 interim efficacy analyses when 30% and 60% of the 90-day data are available and using Haybittle-Peto stopping boudaries. The α-level for the final analysis will be the conventional significance level (α = 0.0482).

11. SUBSTUDIES OF SECONDARY PREVENTION

Patients who survive an AIS are at high risk of a recurrent event, which is often more disabling, fatal and costly. The risk of recurrent AIS is highest within the first month after the initial event, with event frequencies being approximately 1% at 6 hours, 5% at 7 days and 10% at 14 days.[39-41] Moreover, recurrent AIS constitute a substantial proportion (25-30%) of all preventable strokes, which highlights the importance of effective secondary prevention.[42] Immediate and sustained implementation of appropriate secondary prevention strategies in patients with first-ever AIS is an important aspect of efforts to reduce the burden of AIS.

11.1 Timing of initiating anticoagulation therapy in AIS patients with MT

11.1.1 Aims

Compared with late initiation of anticoagulation (commence therapy at Day 12±2 of stroke onset), early initiation (commence therapy at Day 4±2 of stroke onset) is superior at improving net benefit by balancing AIS recurrence and bleeding within 90 days in patients with AF-related AIS due to LVO who receive MT.

11.1.2 Background and Rationale

Anticoagulation therapy for secondary prevention in AF-related AIS

Cardioembolic AIS, most often attributable to non-valvular AF, accounts for approximately 13–26% of all AIS,[43, 44] and the frequency is likely to be higher in patients who have MT for LVO.[44-46] Aspirin is less effective than warfarin anticoagulation in preventing recurrent AIS in patients with AIS related to AF.[45] Vitamin K antagonists (VKAs) are, therefore still recommended as first-line therapy in patients with AF in many countries. Compared with aspirin, warfarin with an international normalised ratio (INR) of 2.0-3.0 can significantly reduce the risk of recurrent AIS and systemic embolism (OR 0.49, 95% CI 0.33-0.72), despite an increased risk of major extracranial bleeding events (OR 5.2, 95% CI 2.1-12.8).[45, 46] However, four direct oral anticoagulants (DOACs), apixaban, dabigatran, edoxaban and rivaroxaban, have been approved for stroke prevention in patients with non-valvular AF since 2010.[47-50] Various systematic reviews and meta-analyses have shown that DOACs are at least as effective as VKAs in primary and secondary prevention of stroke, but with reduced risk of ICH.[51, 52]

Current guideline recommendations on timing of initiating oral anticoagulation therapy

Current guidelines are inconsistent in their recommendations regarding timing of initiation of oral anticoagulation therapy after recent AF-related AIS. In 2013, the European Society of Cardiology (EHRA-ESC) introduced '1-3-6-12' rule to guide oral anticoagulation therapy, which was based on observational data suggesting safety in commencing anticoagulation within a

few days and delaying initiation for large infarcts with higher risk of HT.[53] However, such time-points and definitions of stroke severity are based on expert consensus. The AHA/ASA 2018 guidelines recommend a wide window (4-14 days) for commencing oral anticoagulation after symptoms onset in AF-related AIS, based on mainly on the findings of the Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) study,[22, 54] of a prospective cohort of 1029 consecutively enrolled AIS patients and known or newly diagnosed AF. The results indicate that initiating anticoagulants 4-14 days from stroke onset was associated with a significant reduction in primary composite event outcome, compared with initiation either before 4 or after 14 days (adjusted HR 0.53, 95% CI 0.30-0.93).[54] However, no guidelines distinguish between VKAs and DOACs, despite there are substantial differences in the mechanism and pharmacodynamics of these compounds.

Uncertainty over the optimal timing of initiating anticoagulation therapy in patient with acute AF-related ischemic stroke

The optimal timing of OAC following an AIS is unknown. The risks of both early recurrence and HT are highest in the first few days.[55, 56] So initiating OAC in this period could offer benefits, but how much of these offset by early major bleeding is uncertain.[57, 58] Clinicians intend to delay initiation of anticoagulation therapy in those who they suspect are at increasing risk ICH, based on petechial or parenchymal ICH.[58,59] An online survey of UK stroke physicians showed that 95% were uncertain about optimal timing.[44]

Several non-randomised, prospective observational studies have explored the potential risks and benefits of early anticoagulation with DOACs in patients with AF-related AIS. Seiffge et al. assessed the risk of both ICH and recurrent AIS with different initiation time of DOACs during follow-up (at least 3 months) in 204 patients.[60] The study showed the rate of recurrent AIS was 6 times higher than ICH, and there was no significant difference on recurrent AIS between early (<7 days) and late (>7 days) start of a DOAC. cRAF-NOACs, a prospective observational multicentre study, included 1127 AF-related AIS patients treated with DOACs to evaluate the risk of early recurrence and major bleeding within 90 days,[61] showed that the primary outcome occurred in 12.4% of those with DOACs initiated within 2 days after onset, 2.1% between 3 and 14 days, and 9.1% after 14 days (P <0.0001). However, the multivariate model estimated no significant marginal effect with the timing of administration (<3 days as reference, 3-7 days: OR 1.30, 95% CI 0.54-3.71; 8-14 days: OR 1.44, 95% CI 0.36-3.02; >14 days: OR 0.59, 95% CI 0.15–1.95). In addition, Wilson et al. found that compared with late OAC (5 days and onwards or anticoagulation never started), early OAC (4 days or earlier) after AIS/TIA associated with AF was not associated with a significant difference in the rate of the composite outcome of stroke/TIA or death at 90 days, after adjustment for confounding baseline variables.[57]

All these studies suggest that early DOAC administration in patients with AF-related AIS has a low frequency of ICH (including HT). However, these observational studies are limited by indication bias where patients suspected of lower risk of ICH are more likely to receive early treatment. They are also biased towards the inclusion of mild-moderate severity of stroke (median NIHSS scores 3–8) and small infarcts (generally less than one third of affected arterial territory).

Ongoing trials of early versus late initiation of DOAC anticoagulation therapy

Several ongoing RCTs are investigating the balance of risk and benefit of early versus late initiation of DOACs in patients with a recent AF-related ischemic stroke (Table 3): ELAN (NCT03148457; Switzerland), OPTIMAS (EudraCT, 2018-003859-38; UK), TIMING (NCT02961348; Sweden), and START (NCT03021928; USA).[44] All these studies use any

stroke (includes both AIS and ICH), and 3 include mortality, as the primary outcome. A pooled individual patient data meta-analysis of these trials is planned.

Rationale of early initiation of anticoagulation therapy in AF-related AIS patients due to LVO treated with MT

Although the patients who received MT procedure after AIS due to LVO have increasing risk of HT (given having higher average baseline severity, the procedure itself and reperfusion injury), early initiation of anticoagulation therapy may bring bigger net benefit via reduced risk of recurrent AIS and improving patient compliance when medication is started in hospital. In addition, successful reperfusion after MT and usage of DOACs may further reduce the risk of HT through decreasing infarct size and increasing safety.

Summary

Although the effectiveness of anticoagulation for secondary prevention of recurrent AIS is well recognized, the optimal timing of this therapy after symptom onset remains uncertain due to the perceived increased risk of ICH. Although several ongoing trials may provide robust evidence to assess the safety and efficacy of early DOAC treatment, it is unlikely that they will recruit an adequate sample of high-risk patients who have received MT procedure. We have included a specific substudy to determine the balance of effectiveness and safety of early initiation of anticoagulation in patients with AF-related AIS who receive MT.

Table 3 Summary of ongoing RCTs investigating early versus late initiation of DOACs in patients with recent AF-related ischemic stroke

	Sample size	Intervention (early initiation)	Control (late initiation)	Follow-up period	Primary Outcomes	Patients with HT included	NIHSS Exclusion criteria	Estimated end of study
ELAN NCT03148457	2000	<48 h after symptom onset (minor and moderate stroke) or at day 6 (±1 day) after symptom onset (major stroke)*	Current recommendations (ie, minor stroke after day 3 [±1 day], moderate stroke after day 6 [±1 day] and major stroke after day 12 [±2 days])*	30 days (secondary outcomes after 90 days)	Composite outcome (major bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death, or a combination of these outcomes)	Yes	No Exclusion criteria	Oct 2021
OPTIMAS NCT03759938 EudraCT, 2018-003859-38	3474	≤4d	7-14d	90 days	Composite outcome at 90 days (combined incidence of recurrent symptomatic ischaemic stroke, sICH [including extradural, subdural, subarachnoid and ICH, and HT of the qualifying infarct], and systemic embolism)	Yes	No Exclusion criteria	2021–22
TIMING [62] NCT02961348	3000	≤4 days after acute ischaemic stroke	5–10 days after acute ischaemic stroke	90 days	Composite outcome (recurrent ischaemic stroke, sICH, or all-cause mortality, or a combination of these outcomes)	Yes	No Exclusion criteria	Dec 2020
START NCT03021928	1500 (1000 patients with mild or moderate stroke, 500 with severe stroke)	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke†	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke†	30 days (secondary outcomes after 90 days)	Composite of any CNS haemorrhagic or other major haemorrhagic events and the ischaemic events of stroke or systemic embolism within 30 days of the index stroke	Yes	Score >3 and score <23	Aug 2021

NIHSS: National Institutes of Health Stroke Scale; sICH: symptomatic intracranial haemorrhage.
ELAN=Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients with Atrial fibrillation. OPTIMAS=OPtimal TIMing of Anticoagulation after AF-associated acute cardioembolic ischaemic Stroke. TIMING=Timing of oral anticoagulant therapy in acute ischemic stroke with atrial fibrillation. START=Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation.
*Small infarct size is defined by lesions smaller than 1·5 cm in the anterior or posterior circulation; medium infarct size by lesions in a cortical superficial branch of middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, or in a cortical superficial branch of the anterior cerebral artery; large infarct size by lesions that involve the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery, in two cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than one artery territory.
†Minor stroke is defined by a NIHSS score <8, mild stroke by a NIHSS score of 8–15, and severe stroke by a NIHSS score >15, as per the European Society of Cardiology and European Heart Rhythm Association definitions

11.1.3 Study design

This substudy - **Timing of anticoagulation** - is a pilot study imbedded in the main ENCHANTED2 study. Consent will be obtained prior to MT procedure, but randomisation will be undertaken post-MT at the same time of the main study, according to separate eligibility criteria. Randomised allocation (1:1 ratio) of intervention will be done via the same central, automated, mobile APP-based randomisation software as the main study, according to minimized method stratified by site and randomisation of BP intervention.

Study population

Among all patients are randomised into the main trial, those eligible for this substudy are those with a final diagnosis of AF-related AIS.

Inclusion and exclusion criteria

To be eligible for inclusion for this sub-study, patients enrolled in the main study **ARE** much satisfy all of the following criteria:

a) AIS due to permanent, persistent, or paroxysmal spontaneous AF documented previously or diagnosed during hospitalization
b) Agreement of treating physician to prescribe either a DOAC or warfarin anticoagulation
c) Provision of written informed consent (or via an appropriate proxy, according to local requirements)

Patients will **NOT** be eligible if there is one or more of the following:

a) AF due to clear reversible causes (e.g. thyrotoxicosis, pericarditis, recent surgery, acute myocardial infarction)
b) Patients with serious bleeding in the last 6 months or is at high risk of bleeding (e.g. active peptic ulcer disease, platelet count <100,000/mm^3 or hemoglobin <10 g/dl or INR $\geqslant$1.7, documented hemorrhagic tendencies or blood dyscrasias)
c) Specific contraindication to any form of oral anticoagulation

Treatment allocation

Attending clinicians are required to consider their level of clinical uncertainty over the balance of potential benefits and risks pertaining to the level of anticoagulation treatment in each particular patient. Investigators are encouraged to adhere to study protocols, provide active care, but are free to modify a patient's treatment as required according to clinical judgment. A DOAC is the preferred recommendation, but a VKA is accepted if DOACs are not available or not affordable for patients. Postponing, stopping or restarting anticoagulation therapy is at the discretion of the attending clinician if the patient suffers from an adverse bleeding event.

Early initiation of oral anticoagulation therapy

Early treatment will be started at Day 4±2 of stroke onset.

Late initiation of oral anticoagulation therapy

Late treatment will be started as per current recommendations at Day 12±2 of stroke onset.

11.1.4 Study outcomes

Primary outcome

Composite of recurrent AIS, sICH, systemic embolism and/or death within 90 days after randomisation

Secondary outcomes are:

a) Functional outcomes defined as a shift (improvement) in scores on the mRS at 90 days

b) Any ICH reported by investigators or after central adjudication of relevant brain imaging within 90 days after randomisation

c) sICH, in which ICH is associated with substantial neurological deterioration or death according to various definitions within 90 days

d) Death or disability by scores 3-6 on the mRS at 3 months

e) Separately on death and disability at 3 months

f) Length of hospital stay

g) HRQoL by the EuroQoL at 3 months

11.1.5 Sample size

In this and the other substudy, the aim is to recruit as many patients to inform the sample size estimates for the main study. Our preliminary sample size calculation to provide a reliable assessment of the treatment effect is outlined below.

The results of Pre-TIMING study in Sweden revealed 12% of primary outcomes (4% of recurrent ischemic stroke, 3% of sICH, and 4% of all-cause mortality) in AF-related AIS patients with OAC therapy at 90 days.[62] Given more severe patients are being enrolled in ENCHANTED2, the event rate is expected to be around20%. A sample size of 2418 subjects provides 90% power to detect a 5% absolute (25% relative) risk reduction on a composite outcomes at 90 days between the randomised groups in AIS patients with successful post-MT reperfusion.

11.1.6 Data collection and follow up

Day 90 (± 7d)

The adherence of the anticoagulation therapy in each randomised group will be collected through 90-day follow-up.

11.2 Duration of dual antiplatelet therapy (DAPT)

11.2.1 Aims

Compared with a standard duration of DAPT (3 months), a short duration (6 weeks) of DAPT is at least as effective (‘not inferior ‘) in reducing the risk of recurrent stroke over 12 months, in AIS patients with LAA who undertook MT (i.e. corresponding null hypothesis is that short duration of treatment is inferior than standard duration on this outcome).

11.2.2 Background and rationale

The effectiveness of APT for the secondary prevention of AIS is well recognized,[63] but the efficacy and safety of DAPT in MT-LVO patients remains controversial.[64, 65] Whilst European guidelines do not recommend long-term DAPT in AIS patients, AHA/ASA guidelines (2018) recommend 21-days of DAPT with aspirin and clopidogrel commenced within 24 hours of symptom onset with minor stroke (Class IIa; Level of Evidence B) based on the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) [41] and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)[69] trials. In CHANCE, 5170 Chinese minor AIS/high-risk TIA patients were randomly assigned to either DAPT (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or placebo plus aspirin (75 mg per day for 90 days), to show DAPT was superior in reducing the risk of recurrent stroke at 90 days (HR 0.68,

95% CI 0.57-0.81; P <0.001), with no significant increase in ICH risk (HR 1.41, 95% CI 0.95-2.10; P = 0.09) compared to monotherapy. The multinational POINT trial showed a 28% reduction in stroke recurrence with DAPT compared to aspirin monotherapy, but major bleeding events were double.[66] A meta-analysis published in 2013 included 14 RCTs of DAPT versus aspirin among 9102 AIS/TIA patients, showed that DAPT significantly reduce the risk of recurrent stroke in 3 months (RR 0.69, 95% CI 0.6-0.8), without increasing the major bleeding events (RR 1.35, 95%CI 0.7-2.59).[65] However, a recent meta-analysis including POINT further explored the optimal duration of DAPT to show that short-term (one month) reduced the risk of recurrent AIS (RR 0.53; 95% CI 0.37-0.78) without a significant increased the risk of major bleeding (RR 1.82; 95% CI 0.91-3.62).[67]

The application of these findings to LVO/MT patients is limited as they are confined to those with minor AIS (NIHSS < 4) or high-risk TIA as an acute therapy in an unstable plaque. The only trial focussed on the efficacy of DAPT in patients with LAA was Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS), which included patients with recent AIS/TIA attributed to 70-99% stenosis of a major intracranial artery, randomly assigned to aggressive medical management alone (including with a dose of 325 mg aspirin and 75 mg clopidogrel per day for 90 days) or aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS) with the use of the Wingspan stent system.[68] Enrolment was stopped after 451 patients were randomised because the 30-day rate of stroke or death in the PTAS group was significantly higher than medical-management group (14.7 vs. 5.8%, P =0.002), indicating aggressive medical management was superior to PTAS alone. Despite the lack of direct evidence, many clinicians prescribe DAPT to those patients with LAA where there is high risk of recurrent stenosis, for example intra-MT endothelial trauma or placement of a stent to maintain reperfusion. The standard duration of DAPT in such cases is 3 months post-MT. A shorter duration of DAPT for LAA patients post-MT may provide greater benefit over ongoing risk of major bleeding.

In summary, the efficacy and safety of DAPT for secondary prevention as well as the optimal duration in patients with major stroke remains unresolved. This imbedded substudy aims to determine the effectiveness of a short duration of DAPT in patients with LAA who receive MT.

11.2.3 Study design

This substudy – **Duration of DAPT** - is a pilot study imbedded in the main ENCHANTED2 study. Consent will be obtained prior to MT procedure, but randomisation will be undertaken post-MT at the same time of the main study, according to separate eligibility criteria. Randomised allocation (1:1 ratio) of intervention will be done via the same randomisation system as the main study, according to minimized method stratified by site and randomisation of BP intervention. The patients will be either allocated to short duration (6 weeks) or standard duration (3 months) of DAPT within 48 hours after AIS onset, and to be maintained on antiplatelet monotherapy (aspirin or clopidogrel) thereafter.

Study population

All patients randomised in the main trial, who have a final diagnosis of LAA-related AIS will be considered for enrolment in this sub-study. *In comparison to all other randomised patients, patients included in this substudy are followed up for 12 months.*

Inclusion and exclusion criteria

To be eligible for inclusion for this substudy, patients who has been enrolled into the main study **ARE** to still satisfy all of the following criteria:

a) Final diagnosis of LAA confirmed by imaging during MT procedure

b) Provision of written informed consent (or via an appropriate proxy, according to local requirements)

Patients will **NOT** be eligible if there is one or more of the following:

c) Definite contraindication to both aspirin and clopidogrel

Treatment allocation

Short duration of DAPT

The patients will receive oral (including nasogastric if required) DAPT (aspirin 100 mg and clopidogrel 75 mg per day) for **6 weeks** within 48 hours after stroke onset if no PH confirmed by imaging after MT. If the patient is intolerance with aspirin or clopidogrel, cilostazol / dipyridamole can be used as a substitute.

Standard duration of DAPT

The patients will receive oral (including nasogastric if required) DAPT (aspirin 100 mg and clopidogrel 75 mg per day) for **3 months** within 48 hours after stroke onset if no PH confirmed by imaging after MT. If the patient is intolerance with aspirin or clopidogrel, cilostazol / dipyridamole can be used as a substitute.

11.2.4 Study outcomes

Primary outcome: new stroke event (ischaemic or haemorrhagic) over 12 months

Secondary outcomes are:

a) Major adverse cardiovascular events (MACE), defined as a combination of recurrent AIS, myocardial infarction (MI) and all-cause mortality over 3 and 12 months

b) Recurrent AIS over 3 months and 12 months

c) Any ICH reported by investigators or after central adjudication of relevant brain imaging over 3 months and 12 months

d) sICH, in which ICH is related to substantial neurological deterioration or death according to various definitions over 3 months and 12 months

e) Death or disability by shift analysis of scores on the mRS at 3 months and 12 months

f) Separately on death and disability at 3 months and 12 months

g) Neurological deterioration ≥4 points decline in NIHSS score over 7 days after randomisation

h) Length of hospital stay

i) HRQoL by the EuroQoL at 3 months and 12 months

11.2.5 Data collection and follow-up

Day 365 (±1 month)

These assessments are to be undertaken by an investigator who was not involved in the clinical management of the patient, and blind to the randomised treatment allocation. On 365 ± 30 days, all surviving patients will be evaluated through a telephone interview or at a face-to-face consultation. Use of BP lowering agents **(see Appendix 1)**, antiplatelet agents, and adherence will be recorded. In addition to the mRS, cardiovascular events (CV death, non-fatal stroke, non-fatal myocardial infarction, major bleeding), HRQoL (using the EQ-5D) will be assessed.

11.2.6 Sample size

In this and the other substudy, the aim is to recruit as many patients to inform the sample size estimates for the main study. Our preliminary sample size calculation to provide a reliable assessment of the treatment effect is outline below.

Ma et al. reported the proportion of post-stenting events of recurrent AIS and ICH over 12 months was 5.8% among patients with symptomatic intracranial atherosclerotic stenosis in China.[69] Considering on a broader inclusion of hospital sites and severe study population, the event rates were set up as 10%. As recommended by the United States Food and Drug Administration (FDA), the clinical margin representing the largest acceptable inferiority of the test to control is set at 50% of the margin of the excess risk. In this study, a relative non-inferiority margin of 40% (i.e. risk ratio 1.4) was used to provide assurance that short duration of DAPT retains at least 60% of the effects of reducing stroke recurrence risk compared with standard duration. A sample size of 2366 provides 90% power (1-sided α =0.025) to reject a non-inferiority margin of 1.4 from an expected event rate of 10% in the standard duration arm and assuming no true difference between the two durations.

12. PUBLICATION, REPORTS AND DATA SHARING

Publication of the main reports from the study will be in the name of the ENCHANTED2 Investigators. Full editorial control will reside with a Writing Committee approved by the SC.

Investigators have the right to publish or present the results of the study. However, as this is a multi-site academic study, investigators agree not to publish or publicly present any interim results of the study without the prior written consent of the SC. Investigators further agree to provide the SC at least 30 days prior to submission for publication or presentation, review of copies of abstracts or manuscripts (including without limitation, text and PowerPoint presentation slides and any other texts of transmissions or media presentations) that report any results of the study.

The SC shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts. The SC also have the right to review and comment on the data analysis and presentation with regard to the accuracy of the information, the protection of the rights of individuals, and to ensure that the presentation is fairly balanced and in compliance with appropriate regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality, the particular investigator(s) will agree to meet with members of the SC at the clinical site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any disagreements.

Writing Committees will be formed from members of the various committees, statisticians, research fellows and investigators. They will prepare the main reports of the study to be published in the name of “ENCHANTED2 Investigators” with credit assigned to the collaborating investigators and other research staff. Presentations of the study findings will be made at national and international meetings concerned with the management of stroke, cardiovascular disease, and hypertension.

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship that follow:

1 Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;

2 Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;

3 Authors must provide approval of the final draft version of the manuscript before it is submitted to the journal for publication.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per ICMJE guidelines for acknowledgement.

At the completion of the study, requests for secondary analysis will be in accordance with a defined protocol from an experience research group with an agreed analysis plan with The George Institute. In addition, data will be shared with other investigators on the study, and investigators from other institutions around the word, according to a strict data sharing agreement.

Data sharing will be available from 12 months after publication of the main results. The consent form will include information as to the purpose of this activity. Investigators are to make a formal request for data sharing through the Research Office of TGI, CHINA and get approval from the SC.

13. ORGANISATION

Central coordination is from TGI, CHINA, and the study will be overseen by an International SC comprised of world experts in the fields of stroke, hypertension, neurology, geriatrics, cardiovascular epidemiology and clinical trials. The CCC will also be supported by key grant holders and regional experts in the OC. The CCC communicates with regional committees and approximately 80-100 participating hospitals in China in the first instance, and up to 50 sites outside of China depending on funding. Sites will be administratively tied through a structure designed to enhance effective communication and collaboration as well as monitor and maintain operations through adherence to a common protocol.

13.1 Steering Committee (SC)

Responsibilities: Overall responsibility for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The SC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. Provisional list of SC is given below:

Professor Craig Anderson (Co-Principal Investigator), The George Institute for Global Health, China; University of New South Wales, Australia

Professor Jianmin Liu (Co-Principal Investigator), Changhai Hospital, China

Dr Lili Song, (Co-Senior clinical lead) The George Institute for Global Health, China; University of New South Wales, Australia

A/Prof Pengfei Yang (Co-Senior clinical lead), Changhai Hospital, China

Additional SC members, and international advisors, will be invited to join at the discretion of Professors Liu and Anderson according to their expertise and contribution to successful conduct for the study, within and outside of China.

13.2 Central Coordinating Centre (CCC)

The CCC is at TGI, CHINA

Responsibilities: Day to day management of the study, data and project management, committee coordination, assistance with ethics committee applications, protocol and procedures training for participating centres, initiation visits to participating centres, monitoring of data quality and adherence to applicable guidelines and regulations, preparation of study data for analysis and publication.

13.3 RCC

Responsibilities: Provide advice to the CCC on regional issues relevant to the set up and management of the study. In conjunction with the CCC, provide assistance and support and monitor study progress at regional participating centres, including data quality and adherence to the study protocol.

13.4 Imaging Adjudication Committee (Core Lab/Brain Imaging Analysis)

Responsibilities: To measure haemorrhagic complications (hematoma volume) and ischemia/infarction on all de-identified and blinded brain imaging scans (blinded by allocation group and timing of scan).

13.5 Clinical Endpoints Committee

Responsibilities: Review blinded study outcomes to ensure endpoints meet the consistent diagnostic criteria in line with pre-determined criteria.

13.6 Data Safety Monitoring Board (DSMB)

Responsibilities: Review the safety, ethics and outcomes of the study.

13.7 Participating Centres

Neurology Wards / Neurosurgery Departments / Acute Stroke Units

Responsibilities: Overall management of study at own hospital in line with the study protocol; study nurse recruitment and orientation; protocol education of colleagues, patient recruitment, data collection and data transfer to the CCC, data query resolutions, liaison with local Hospital Research Ethics Committee/Institutional Review Board, adherence to local ethics guidelines and reporting requirements, adverse event reporting to local Hospital Research Ethics Committee/Institutional Review Board and to the CCC in accordance with protocol.

14. FUNDING

Funding for the study is part of a consortium, with research grants held by TGI, CHINA and Changhai Hospital. This study has received initial funding from a Program Grant from the National Health and Medical Research Council (NHMRC) of Australia (APP1149987), China National Health Commission Stroke Prevention Committee “China Stroke Prevention and Intervention Project” (GN-2020 R0008), and grants from Changhai Hospital (including “National Clinical Key Specialist Construction Project’ 2016). This study also receives funding support from Takeda China.

15. TIMELINES

Milestones for main study	2019	2020	2021	2022	2023
Protocol design and materials development	→				
Sign contract with investigators		→			
Set-up of regional centres		→			
Ethics applications		→			
Training sites		→	→		
Commence recruitment and intervention		→	→	→	
Outcomes assessment		→	→	→	
Close out				→	
Analysis and Results					→
Presentation / publication of main result					A

16. REFERNCES

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17. APPENDIX

Appendix 1 - BP management protocol

Appendix 1A - BP protocol for centres with Urapidil (China)

Intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP <120mmHg** achieved within 1 hour after randomisation
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during active treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Urapidil (IV)	• If SBP ≥ 120 mmHg and HR >55 bpm, repeat 10-25 mg IV bolus q5 mins until target SBP reached (<120mmHg) or HR <55 bpm • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker**
Hydralazine (IV)	• Hydralazine test dose: 5 mg IV bolus over 1 minute • If SBP ≥ 120 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still ≥ 120mmHg, give 10 mg IV bolus q 5 mins until target SBP reached • Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg
Glyceryl Trinitrate (topical)	If BP persistently ≥ 120 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24 hour (≈ 200-400 µg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently ≥ 120 mmHg: • Urapidil infusion 5-30 mg/hour • If target still not reached ADD infusion of hydralazine 50-150 µg/min OR glyceryl trinitrate 1-100 µg/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP 100-120 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h
IV treatment prn	If SBP exceeds 120mmHg at any point: • Give Urapidil (10-25 mg) and/or hydralazine (10-20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later • If SBP is 100-120mmHg, Urapidil 10-25 mg (dose dependent on initial response) should be administered q 6 hours for the first 24 hours after symptom onset (total of 3 doses) • If SBP ≤ 100 mmHg, cease therapy • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker** • Note: urapidil and hydralazine may be used together during the maintenance phase

Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics ± previous antihypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; µg/Kg/min – micrograms per kilogram per minute; µg/min – micrograms per minute.

Appendix 1B - BP protocol for centres with Phentolamine (China)

Intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP < 120 mmHg** reached within 1 hours after randomisation
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during active treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Phentolamine (IV)	• If SBP ≥120 mmHg and HR >55 bpm, repeat 5 mg IV push q 5 mins until target SBP reached (<120mmHg) or HR <55 bpm • If HR increases by >15 bpm or is >90 bpm, add IV beta blocker
Hydralazine (IV)	If BP persistently ≥ 120 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP ≥ 120 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still ≥120mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently ≥ 120 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 µg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently ≥ 120 mmHg: • Phentolamine infusion 0.2-5 mg/minute • If target still not reached, ADD infusion of hydralazine 50-150 µg/min OR glyceryl trinitrate 1-100 µg/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP 100-120 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h
IV treatment prn	If SBP exceeds 120mmHg at any point: • Give Phentolamine (5 mg) **and/or** hydralazine (10-20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later • If SBP is 100-120mmHg, Phentolamine 5 mg (dose dependent on initial response) should be administered q 6 hours for the first 24 hours after symptom onset (total of 3 doses) • If SBP ≤ 100 mmHg or HR < 55 bpm, then cease treatment. • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker** • Note: phentolamine and hydralazine may be used together during the maintenance phase

Oral treatment	Start treatment by 24 hours (use nasogastric if required). • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; µg/Kg/min – micrograms per kilogram per minute; µg/min – micrograms per minute.

Appendix 1C - BP protocol for centres with Labetalol

Early intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP < 120 mmHg** reached within 1 hour after randomisation
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during active treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Labetalol (IV)	• If SBP ≥ 120 mmHg and HR >55 bpm, repeat 20 mg IV push q 5 mins until target SBP reached (< 120mmHg) or HR <55 bpm; increase to 40 mg bolus if required • Maximum labetalol dose: 300 mg / 24 hours
Hydralazine (IV)	If BP persistently ≥ 120 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP ≥ 120 mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still ≥ 120mmHg, give 10 mg IV bolus q 5 mins until target SBP reached. Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg/24 hours
Glyceryl Trinitrate (Topical)	If BP persistently ≥ 120 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 µg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently ≥ 120 mmHg: • Labetalol infusion 2-8 mg/min to a maximum of 300 mg/24 hours (consider this if response to labetalol boluses is adequate but brief) • If target still not reached, ADD infusion of hydralazine 50-150 µg/min OR glyceryl trinitrate 1-100 µg/Kg/min • OR start infusion of Nicardipine 5-15 mg/hour
MAINTENANCE therapy	
BP Target	Maintenance of SBP 100-120 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
IV treatment prn	If SBP exceeds 120mmHg at any point: • Give Labetalol (20-40 mg) **and/or** hydralazine (10-20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later • If SBP is 100-120mmHg, Labetalol 10-40 mg (dose dependent on initial response) should be administered q 6 hours for the first 24 hours after symptom onset (total of 3 doses) • If SBP ≤ 100 mmHg or HR < 55 bpm, then cease treatment • Maximum labetalol dose: 300 mg/24 hours

- **Note: labetalol and hydralazine may be used together during the maintenance phase**

Oral treatment	Start treatment by 24 hours (use nasogastric if required) • If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with labetalol and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; µg/Kg/min – micrograms per kilogram per minute; µg/min – micrograms per minute.

Appendix 1D - BP protocol for centres with Hydralazine

Early intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP < 120 mmHg** reached within 1 hour after randomisation
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during active treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Hydralazine (IV)	• If BP persistently ≥ 120 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP ≥140mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still ≥ 120mmHg, give 10 mg IV bolus q 5 mins until target SBP reached • Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg
Metoprolol (IV)	If BP persistently ≥ 120 mmHg: • ADD Metoprolol 5 mg IV bolus over 3-5 minutes, repeat 5mg bolus in 5 minutes x 2 if necessary but do NOT give if HR < 55bpm
Glyceryl Trinitrate (Topical)	If BP persistently ≥ 120 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 µg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently ≥ 120 mmHg: • Start infusion of hydralazine - 50-150 µg/min • If target still not reached, ADD infusion of glyceryl trinitrate 1-100 µg/Kg/min • OR start infusion of Nicardipine 5-15 mg/hour
MAINTENANCE therapy	
BP Target	Maintenance of SBP 100-120 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
IV treatment prn	If SBP exceeds 120mmHg at any point: • Give Hydralazine 10-20 mg boluses. BP and HR should then be recorded 5 and 15 minutes after each bolus • If SBP is 100-120mmHg, give further Hydralazine 10-20 mg boluses (dependent on initial dose) q 6 hours for first 24 hours (total of 3 doses) • If SBP ≤ 100 mmHg or HR <55 bpm, then cease treatment
Oral treatment	Start treatment by 24 hours (use nasogastric if required)

- If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; µg/Kg/min – micrograms per kilogram per minute; µg/min – micrograms per minute.

Appendix 1E - BP protocol for centres with Clevidipine

Early intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP < 120 mmHg** reached within 1 hour after randomisation
Monitoring	• Continuous HR monitoring • Record BP/HR q 5 mins during active treatment, then q 15 min for first hour, q 30 min for next 5 hours and then hourly to 24 h
Clevidipine (IV)(requires ICU admission)	If BP persistently ≥120mmHg: • Initial Clevidipine dose: 2mg/h iv in first 1.5min • If SBP≥120mmHg, add double dosage ever 2-10min(4,8,16 until 32mg/h) • Max dosage = 32mg/h
Hydralazine (IV)	If BP persistently ≥ 120 mmHg: • ADD Hydralazine with a test dose: 5 mg IV bolus over 1 minute • If SBP ≥140mmHg, repeat 5 mg IV bolus in 5 minutes • If SBP still ≥ 120mmHg, give 10 mg IV bolus q 5 mins until target SBP reached • Increase to 20 mg bolus if required • Maximum hydralazine dose = 240mg
Glyceryl Trinitrate (Topical)	If BP persistently ≥ 120 mmHg: • ADD topical glyceryl trinitrate (paste or patch) at a rate of 5-10 mg/24hour (≈200-400 µg/hour). NB: also known as topical nitroglycerin
Continuous IV Infusions (requires ICU admission)	If BP persistently ≥ 120 mmHg: • ADD infusion of hydralazine - 50-150 µg/min OR glyceryl trinitrate 1-100 µg/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP 100-120 mmHg
Monitoring	Once SBP is under target (confirmed by 4 readings 15 minutes apart): • Record BP/HR q 30 minutes for 5 hours and then q 1 h for 18 h.
IV treatment prn	If SBP exceeds 120mmHg at any point: • DOUBLE the dose of Clevidipine every 2-10 minutes (4, 8, 16 and then maximum dose of 32 mg/hour) • If SBP is 130-140mmHg, Keep the dose of Clevidipine • If SBP < 120 mmHg or HR < 55 bpm, then HALVE the dose of Clevidipine every 2-10 minutes and then cease treatment • **If HR increases by >15 bpm or is >90 bpm, add IV beta blocker**
Oral treatment	Start treatment by 24 hours (use nasogastric if required)

- If not contraindicated and no other drug is specifically indicated, start combination therapy of ACEI + diuretics in addition to previous anti-hypertensives

Note: Monoamine oxidase inhibitors are not recommended with this BP lowering agent and phosphodiesterase inhibitors must not be used with GTN.

Key to abbreviations: ACEI – Angiotensin converting enzyme inhibitor; BP – blood pressure; bpm – beats per minute; HR – heart rate; ICU – intensive care unit; q – every; prn – as required; µg/Kg/min – micrograms per kilogram per minute; µg/min – micrograms per minute.

Appendix 1F - Additional IV Medication for BP Use in China

The drugs listed in this Appendix are additional medications for BP lowering that can be used in China sites.

1. Suggested IV medication for BP lowering

1) Esmolol
Dosage and administration:
Bolus or infusion: It is recommended that an initial loading dose of 0.5 milligrams/kg body weight (500 micrograms/kg) infused over a one-minute duration, followed by a maintenance infusion of 0.05 milligrams/kg/min (50 micrograms/kg/min) for the next 4 minutes. If it is efficacious, the maintenance infusion may be continued at 0.05 mg/kg/min. If an adequate therapeutic effect is not observed, repeat the same loading dosage and follow with a maintenance infusion. The maintenance infusion may be continued at 0.05 mg/kg/min or increased step wise (e.g. 0.1 mg/kg/min, 0.15 mg/kg/min or a maximum of 0.2 mg/kg/min) with each step being maintained for 4 or more minutes. The maintenance infusion may be increased to a maximum of 0.3 mg/kg/min. Maintenance dosages above 200 μg/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits.

2) Enalaprilat
Dosage and administration:
Therapy should be individualised. For patients on diuretic therapy, the dosage of enalaprilat should be reduced. Dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. Doses higher than 5 mg every six hours are not suggested.

2. IV medication for BP lowering which can also be used

1) Diltiazem
Dosage and administration:
An initial dose of 10 mg or 0.5 mg - 0.25 mg/kg body weight infused within 3 minutes can be used. Diltiazem should be diluted in normal or glucose solutions to a concentration of 1% before use. This dose can be repeated after 15 minutes. A maintenance infusion of 5 μg - 15 μg/kg/min is also permitted.

2) Nitroglyceride
Dosage and administration:
Nitroglyceride injection 10 mg is diluted in 0.9% normal solution 500 ml or 5% glucose solution 500 ml. The initial dose of nitroglyceride is 5 drops/min, and under close BP monitoring may increase by 5 drops/min every 3-5 minutes. If the dose of 20 drops/min is still not efficacious, 10 drops/min can be added every 3-5 minutes. Doses usually can be from 5 to 50 drops/min.
Note: Phosphodiesterase inhibitors must not be used with GTN.

3) Nimodipine
Dosage and administration:
Nimodipine 50 ml/50 mg should be put in a micro pump and infused in a constant speed 4 ml/hour, once a day. Usually it can be used for 5 to 14 days. Then, change to oral nimodipine. However, the BP lowering effect of oral nimodopine is not obvious.

4) Frusemide
Dosage and administration:
The usual initial dose of furosemide is 20-80 mg. If needed, the same dose can be repeated every 2 hours. The total dosage cannot be more than 1 g/d. If it is not effective, the dose should not be increased, to avoid renal toxicity.

Appendix 1G – Control group-higher BP target

RANDOMISED GROUP	TREATMENT
CONTROL - HIGHER BP TARGET	Use acute intravenous therapy if SBP >180 mmHg, and stop BP lowering agents when SBP ≤ 150 mmHg; Any BP lowering treatment could be used ***ONLY*** if SBP >150 mmHg and maintain a SBP range 140-180 mmHg Oral anti-hypertensives and/or topical nitrates can be used when patient medically stable, as assessed by responsible clinician. Oral treatment should be started by discharge / transfer (**use nasogastric if required**). • If not contraindicated and no other drug is specifically required, start combination therapy ACEI + diuretic therapy in addition to previous anti-hypertensives

Key to abbreviations:

ACEI – Angiotensin converting enzyme inhibitor; SBP – systolic blood pressure

Appendix 2 – Recommendation for MT devices

MT is the background treatment in this trial. All devices listed below (including but not limited to), which are approved by China Food and Drug Administration (CFDA) during the study period, are recommended as first-line devices for MT.

Device name	Manufacturer	Description
Aspiration catheter		
ACE	Penumbra	Aspiration catheter
Retriever		
Solitaire	Medtronic	Stent Retriever
Trevo	Stryker	Stent Retriever
Revive	Cerenovous	Stent Retriever
Aperioa	Acandis	Stent Retriever
Reco	Minitech Medical	Stent Retriever

Appendix 3 - Imaging protocol

It would be desirable to use the same modality for both pre-randomisation and follow-up imaging from the same subject. However if for technical or practical reasons this is not possible, mixed CT and MR acquisitions (eg CT pre-randomisation and MR follow-up) are acceptable.

CT scans should cover the entire brain from the foramen magnum to the vertex with 4–5 mm thick slices through the posterior fossa and 8–10 mm thick for the cerebral hemispheres, with no slice gap. Scans should be windowed on a width of 80 Hounsfield Units (HU) and a centre level of 35–40 HU. All patients (irrespective of treatment allocation) should have a follow-up scan at 24 hours. In addition a repeat scan is required if the patient deteriorates neurologically or ICH is suspected for any reason.

In addition to the diffusion/perfusion MRI or perfusion CT series, any structural MRI (GRE, T2, FLAIR) orCT (spiral CT, etc) sequences acquired at the same time should be included. For CT, spiral CT is to be preferred over CT MPR data or sequential axial CT acquisitions with thick slices. Suggested acquisition parameters are given in Table A1- A4 below.

If angiography (either MR or CT) have also been acquired, these should be submitted as well. Suggested acquisition parameters are given in Table A5 below.

Table A1. Recommended Acquisition Protocol for Perfusion-CT (PCT)

Acquisition Rate	1 image per second, (ideally at one source rotation per second
Total Acquisition Time Base Line Period	40 to 60 seconds 5-10 volumes should be acquired prior to contrast arrival
Kvp and	80 kVp (not 120 kVp)
mAs	100 mAs or higher
Contrast Volume	35-50 mL (with saline flush)
Delivery Rate	4-6 mL per second
Coverage	As dictated by configuration of hardware

Table A2. Recommended Acquisition Protocols for Perfusion-Weighted (PWI) MR Imaging

Sequence	Single-shot gradient-echo echoplanar imaging
TR	TR = 1500 to 2000 ms
TE	TE=35 to 45 ms @ 1.5T TE=25 to 30 ms @ 3T
Flip angle	flip angle =60 to 90° @ 1.5T, 60° @ 3.0T
Baseline	At least 10-12 Baseline images (please note the first few images prior to steady state are discarded)
Coverage	At least 12 slices, with same slice thickness and gap as DWI, increase TR and slice gap to achieve reasonable coverage.

Table A3. Recommended Acquisition Protocols for Diffusion-Weighted (DWI) MR Imaging

Sequence	Single-shot spin-echo echoplanar imaging
TR	Should be at least 4000 ms (but can be larger)
TE	Minimum achievable

Diffusion weighting (b values)	b=0 and 1000 sec/mm2
Coverage	At least 10-12 slices, with same slice thickness and gap as PWI.

Table A4. Example Acquisition Protocol for Spiral CT

Kvp	120
mAs	310
slice collimation	0.75 mm
pitch	0.65
Gantry Rotation	Maximum
Table feed speed	less than 7.5mm per gantry rotation

Table A5. Recommended Acquisition Protocol for CT angiography (CTA) and MR angiography (MRA)

CTA	
Kvp	100
mAs	120
Contrast (volume/type/rate)	50ml Omnipaque 300 at 4ml/sec
Flush (volume/type/rate)	40ml saline at 4ml/sec
delay	15secs
coverage	circle of Willis (upwards)
slice collimation	0.75mm
pitch	1.25

MRA	
Sequence	3D TOF 2 slab HR
TR (ms)	23
TE (ms)	2.7
Flip angle	20°
Locs / slab	32
Slice thickness	1.6
Slice gap	0
Matrix	320 x 224
ΦFOV	1
FOV	16
Slice orient	Straight axial
T-scan	5:46

Brain imaging (CT scan and/or MRI) must be uploaded to the ENCHANTED2 server to be analysed centrally for measurement of ischaemic lesion, measurement of areas of penumbra, sites of vessel occlusion, and haemorrhagic complications. The LCC will keep a hard copy in an uncompressed DICOM format onto a CD-ROM for site monitoring verification.

Brain images are only to be removed from the scanner server after confirmation of receipt of images has been sent to the study centre.

Appendix 4 - Health Scales

Glasgow coma scale (GCS)

Assessment	Measure	Score
Eye opening (E)	4= Spontaneous	
	3= To sound	
	2= To pain	
	1= Never	
Verbal response (V)	5= Oriented	
	4= Confused conversation	
	3= Inappropriate words	
	2= Incomprehensible sounds	
	1= None	
Motor response (M)	6= Obeys command	
	5= Localises pain	
	4= Withdrawal flexion	
	3= Abnormal flexion	
	2= Extension	
	1= None	
TOTAL		**……. / 15**
		(E + M + V)

NB. If the patient is intubated the verbal response should be scored 1.

When scoring the motor response, assess the response for the extremities of side unaffected by partial or complete paralysis.

NIH stroke scale (National Institute of Health Stroke Scale)

Assessment	Response	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	

Assessment	Response	Score
commands. Only the first attempt is scored.		
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal. 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score	0 = Normal symmetrical movement. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).	

Assessment	Response	Score
symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	2 = Partial paralysis (total or near total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:	-
	5a. Left Arm	
	5b. Right Arm	
	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement. 9 = Amputation, joint fusion explain:	-
	6a. Left Leg	
	6b. Right Leg	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case	0 = Absent . 1 = Present in one limb . 2 = Present in two limbs If present, is ataxia in?	

Assessment	Response	Score
of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	**Right arm** 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
	Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain : _____	-
	Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
	Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the	0 = No aphasia, normal. 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response.	

Assessment	Response	Score
preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	
10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	0 = Normal. 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain: _____	
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	
TOTAL		/

Assessment	Response	Score
Additional item, not a part of the NIH Stroke Scale score.		-
A. Distal Motor Function: The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. The patient's first attempts only are graded. Repetition of the instructions or of the testing is prohibited.	0 = Normal (No flexion after 5 seconds). 1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not command is not scored. 2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored.	-
	a. Left Arm	
	b. Right Arm	

Modified Rankin scale (mRS)

		Score
0 =	No symptoms at all.	
1 =	No significant disability despite symptoms, able to carry out all usual duties and activities	
2 =	Slight disability, unable to carry out all previous activities but able to look after own affairs without assistance.	
3 =	Moderate disability requiring some help, but able to walk without Assistance.	
4 =	Moderate severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance.	
5 =	Severe disability, bedridden incontinent, and requiring constant nursing care and attention.	
6 =	Dead.	
		/ 6

European quality of life (EuroQOL)

		Numbers
1. Mobility	1= I have no problems in walking about 2= I have some problems in walking about 3= I am confined to bed	
2. Self-care	1= I have no problems with self-care 2= I have some problems washing or dressing myself 3= I am unable to wash or dress myself	
3. Usual activities (e.g. work, study, housework, family, or leisure activities)	1= I have no problems with performing my usual activities 2= I have some problems with performing my usual activities 3= I am unable to perform my usual activities	
4. Pain/ discomfort	1= I have no pain or discomfort 2= I have moderate pain or discomfort 3= I have extreme pain or discomfort	
5. Anxiety/ depression	1= I am not anxious or depressed 2= I am moderately anxious or depressed 3= I am extremely anxious or depressed	

Appendix 5 - Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically

and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the

participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the nonwritten consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World

Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.