Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215340

This supplement contains the following items:

1. Original protocol in English (page 2 to 77), final protocol in English (page 78 to 154), summary of amendments in English (page 155 to 156)

2. Original statistical analysis plan in English (page 157 to 172), final statistical analysis plan in English (page 173 to 188), summary of amendments in English (page 189)

3. Final protocol in Chinese (page 190 to 261), summary of amendments in Chinese (page 262 to 263)

Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE)

Study Protocol

Supported by

The Ministry of Science and Technology of the People's Republic of China

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Protocol Version 1.0

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PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements.

I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, ICH Good Clinical Practices Guidelines and Institutional Review Board (IRB) requirements.

Clinical Site

_____ _____

Site Principal Investigator Signature Date

Site Principal Investigator Printed Name

CHANCE PROTOCOL SYNOPSIS

Title:	**C**lopidogrel and Aspirin versus Aspirin Alone for the Treatment of **H**igh-risk Patients with **A**cute **N**on-disabling **C**erebrovascular **E**vent (CHANCE): a Randomized, Double-blind, Placebo-controlled Multicenter Trial
Primary Objective:	To assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during first 30 days versus a 3-month regimen of aspirin 75 mg/day alone on reducing the 3-month risk of any stroke (both ischemic and hemorrhagic) when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.
Study Design:	a randomized, double-blind, multicenter, placebo-controlled clinical trial with the primary null hypothesis that, there is no difference in 90-day risk of any new stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during first 30 days versus a 3-month regimen of aspirin 75 mg/day alone when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke. .

Patient Population:

Patients 40 years of age or older with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (with NIHSS ≤ 3) who can be randomized and treated within 24 hours of symptom onset will be enrolled.

Inclusion/Exclusion Criteria:

Inclusion Criteria

- Adult subjects (male or female $\geq$ 40 years)
- Acute non-disabling ischemic stroke (NIHSS$\leq$3 at the time of randomization) that can be treated with study drug within 24 hours of symptoms onset. Symptom onset is defined by the "last see normal" principle.
- TIA (Neurological deficit attributed to focal brain ischemia, with resolution of the deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate-to-high risk of stroke recurrence (ABCD2 score $\geq$ 4 at the time of randomization). Symptom onset is defined by the "last see normal" principle.
- Informed consent signed

Exclusion Criteria

- Diagnosis of hemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major non-ischemic brain disease (e.g., multiple sclerosis) on baseline head CT or MRI.
- Isolated or pure sensory symptoms (e.g.,

numbness), isolated visual changes, or isolated dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI.

- modified Rankin Scale (mRS) Score > 2 at randomization (pre-morbid historical assessment)
- NIHSS≥ 4 at randomization
- Clear indication for anticoagulation (presumed cardiac source of embolus, e.g., atrial fibrillation, prosthetic cardiac valves known or suspected endocarditis).
- Contraindication to clopidogrel or aspirin.
  - Known allergy
  - Severe renal or hepatic insufficiency
  - Severe cardiac failure, asthma
  - Hemostatic disorder or systemic bleeding
  - History of hemostatic disorder or systemic bleeding
  - History of thrombocytopenia or neutropenia
  - History of drug-induced hematologic or hepatic abnormalities
  - Low white blood cell (<2 x109/l) or platelet count (<100 x109/l).
  - Use of thrombolysis within 24 hours prior to randomization
- History of intracranial hemorrhage.

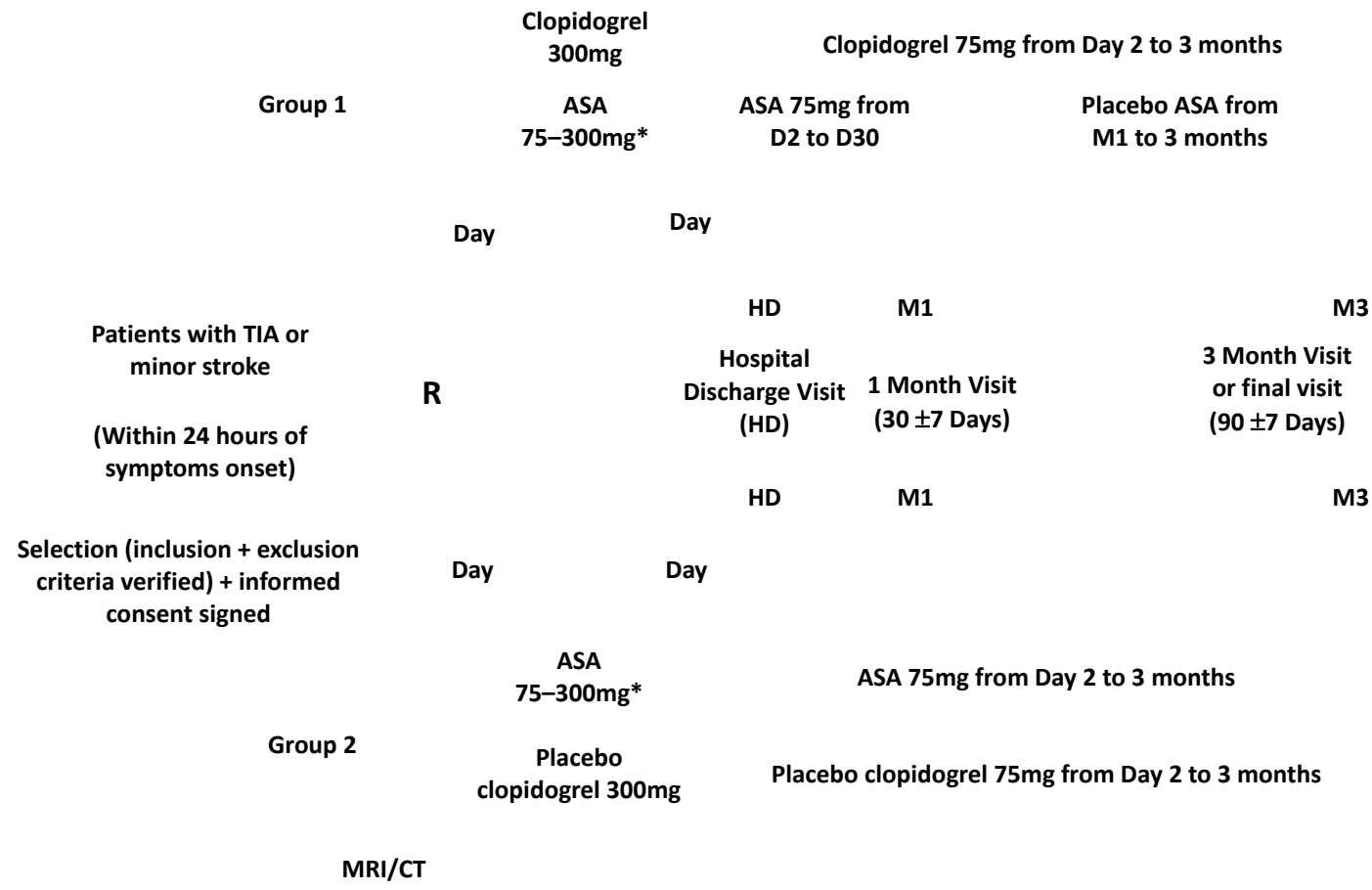
- Anticipated requirement for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function.
- Current treatment (last dose given within 10 days before randomization) with heparin therapy or oral anti coagulation.
- Gastrointestinal bleed or major surgery within 3 months.
- Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months (if clinically indicated, vascular imaging should be performed prior to randomization whenever possible)
- Scheduled for surgery or interventional treatment requiring study drug cessation.
- TIA or minor stroke induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy < 3 months.
- Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- Currently receiving an investigational drug or device.

Randomization:	The randomization code list will be generated centrally by a Contract Research Organization (CRO). The patient kits will be packaged in accordance with this randomization code list. During the treatment period, the patient will receive study medication corresponding to either the clopidogrel / ASA group or the ASA group using a randomization ratio of 1:1. The treatment number will be allocated using a centralized treatment allocation system (Inter-voiceResponse System, IVRS) on D1 (baseline visit). Before randomizing a patient, the investigator will have to contact the IVRS and give some information (such as study number, patient date of birth and initials, study site, and time between symptom onset and randomization). A treatment number will then be given to the investigator, who will give the first box of the corresponding package to the patient.
Primary Endpoint:	Percentage of patients with new stroke (ischemic or hemorrhage) at 3 months.
Study Duration for Each Subject:	Each subject is followed for 90 days from randomization; the trial will be completed in 3 years.
Number of Centers:	Up to about 80 investigational sites in the China in Clinical Research Network.

Sample Size:	Total sample size for the study is 3,800 subjects.
Primary Statistical Analysis:	The time to first new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period for the ITT Population will be summarized by treatment group using Kaplan-Meier estimates. The hazard ratio for the treatment comparison will be derived using a Cox's proportional hazards model, including the pooled study center as a random effect. The hazards ratios with 95% CI will be reported.

1 STUDY FLOWCHARTS

1.1 Graphical Study Design



*Open label ASA: at the discretion of the investigator. The represents the total dose given on D1 (between 75-300 mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day

Figure 1. Graphical study design of CHANCE

1.2 Schedule of Activities and Assessments

Measurements	Screening Visit	Treatment Period				
		Randomization Day 1	Hospital discharge	1 month visit D30 ±7 days	Final Visit D90±7 days	Event Visit
Demographic Characteristics	x					
Modified Rankin Score	x		x	x	x	x
NIHSS	x		x	x	x	x
ABCD2 score (for TIA)	x					
Focused Medical History	x					
Current Medications	x		x	x	x	x
CT/MRI Scan	x*					
Laboratory tests**	x*					x
ECG	x*					x
Inclusion/Exclusion	x					
Informed Consent signed	x					
Randomization (IVRS)	x					
MRI Scan	x***				x***	x
Blood Sample		x****				
EuroQol (EQ-5D)					x	
1st treatment pack given		x				
2nd treatment pack given				x		

AEs/ SAEs			x	x	x	x
Treatment compliance			x	x	x	x

* Standard assessment: Expense not from research funding during baseline period

** Include: Blood routine test (including WBC count, Neutrophil count, Hemoglobin, platelet count, etc.), Blood coagulation, fasting plasma glucose, Hepatorenal function (including Creatine, Serum transaminase).

*** Include: T1+T2+DWI+MRA+Flair+T2*. MRI Scan needed only for subgroup would be completed before/after randomization according to the condition at centers.

****Blood sample needed only for subgroup would be collected as soon as possible after randomization.

2 BACKGROUND AND RATIONAL

2.1 The burden of acute non-disabling cerebrovascular event in China

China bears the biggest burden of cerebrovascular diseases in the world, not only because of its huge population but also the propensity for cerebrovascular diseases; the number of patients who die from cerebrovascular diseases is more than three times that from cardiovascular diseases [1, 2].

Acute non-disabling cerebrovascular event, including transient ischemic attack (TIA), defined as a mini-stroke that symptoms last less than 24 hours, and acute ischemic minor stroke, defined as an ischemic stroke with NIH Stroke Scale score ≤3, is common and often a precursor of a disabling stroke. Ischemic cerebrovascular event i.e. ischemic stroke (IS) and TIA became the predominant cerebrovascular diseases subtype, it was estimated that over 2 million new stroke events occurred each year in China [1, 3], and data from the China National Stroke Registry (CNSR), a national hospital-based registry across China showed that there were about 65% patients with ischemic stroke, and of these, more than 10% were minor ischemic stroke (unpublished data). So far it has not been reported about the incidence of TIA in China. The incidence of TIA in the United States (US) was approximately 68 per 100,000 to 86 per 100,000 person-years, corresponding to about 300,000 TIAs diagnosed each year [4- 7]. Based on the epidemiological studies in the US, it was estimated that at least 2million new TIA events would be diagnosed each year in China. What is more worrying about is that the incidence and mortality of stroke in the western country were declined yearly since the late 20th century, whereas ischemic stroke has been increasing annually and becomes the second leading cause of death in China.[2, 8- 11]

In addition, recurrence of stroke and other vascular events in patients with an initial acute nondisabling cerebrovascular event is one of the most frustrating medical situations.[12, 13] Several cohort studies have shown that early (3 months) risk of stroke following index transient ischemic attack (TIA) and minor ischemic stroke is much higher than previously

thought, even in patients treated with ASA, the current standard of care. [14- 18] Although comparisons across studies are limited by heterogeneity of study populations and clinical settings, they have shown a 90-day stroke risk of 10% to 20% after TIA or minor ischemic stroke.[14, 15, 18- 23]

2.2 Potential treatments of acute non-disabling cerebrovascular event

There are few established, effective therapies for stroke prevention after acute non-disabling cerebrovascular event. Other than ASA, the only approved drug for acute cerebral ischemic event is intravenous tissue plasminogen activator (tPA) [24]. However, for patients arriving within 3 hours of symtoms onset, the most common reasons for ineligibility for thrombolysis are that the deficit is improving or too mild to warrant treatment, and most patients arrive outside the narrow 3 hour window [25]. Thus, no acute therapy is available for the vast majority of patients with acute non-disabling cerebrovascular event.

Platelet aggregation is an important contributing factor in cerebral ischemia, as in other forms of ischemia. Antiplatelet agents reduce the risk of ischemic stroke in a variety of settings with distinct pathophysiologies (e.g., atrial fibrillation, small-vessel stroke, and large-vessel atherothrombosis) [26- 28].

2.2.1 ASA

ASA is the only anti-platelet agent to have been studied in patients presenting acutely with a cerebrovascular event, but the effect is modest and is reduced by a small increased risk of intracerebral hemorrhage. The CAST and IST studies, each enrolling about 20,000, found that acute treatment with aspirin after ischemic stroke reduced the risk of recurrent ischemic stroke by 30% (an absolute change of 0.7%) with a small increase in intracranial hemorrhage (25% relative and 0.2% absolute increase) over 2-4 weeks of treatment [29- 31]. Thus, aspirin has become the standard of care in the acute treatment of patients with stroke. The optimum dose of aspirin continues to be vigorously argued, but is probably in the range of 50-325 mg/day [32]. Aspirin is also considered standard therapy in TIA, with clopidogrel and aspirin-dipyridamole acceptable alternatives, but none has been tested as acute therapy in this setting. [33- 36]

2.2.2 Dipyridamole

Two trials have demonstrated the efficacy of dipyridamole in preventing stroke recurrence: ESPRIT [37] and ESPS-II [38]. Both tested dipyridamole combined with aspirin and found it superior to aspirin alone. In the ESPRIT trial, there was no increased risk of hemorrhage when dipyridamole was added to aspirin. Neither trial evaluated the acute period after a stroke or TIA (median time to enrollment was >21 days), so safety and efficacy during this time period is unknown.

The PROFESS trial [39, 40] failed to meet the pre-specified non-inferiority criteria for aspirin/extended-release dipyridamole vs. clopidogrel and aspirin/extended-release dipyridamole and clopidogrel had similar rates of recurrent stroke and major vascular events. Major hemorrhagic events, including intracranial bleeds, were more frequent among those treated with aspirin/extended-release dipyridamole, but the absolute risks were low and partially offset by fewer ischemic events. In China, aspirin/extended-release dipyridamole has not been currently approved by the Chinese SFDA, Combination of ASA and Clopidogrel is the exclusive options for the high-risk populations or in the acute setting.

2.2.3 Clopidogrel

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation by blocking the ADP receptor [41- 43], a mechanism independent of the thromboxane-mediated pathway inhibited by aspirin. In the CAPRIE trial, clopidogrel 75 mg/day reduced long-term risk of stroke, myocardial infarction, or vascular death by 8.7% relative to aspirin in patients with vascular disease, without increasing risk of hemorrhage or other major side effects[44]. The trial was not designed to evaluate clopidogrel as an acute therapy, and no trial has evaluated the efficacy of clopidogrel after TIA.

Clopidogrel may be useful as an acute intervention after vascular events. With a loading dose of 300 mg, clopidogrel produces platelet inhibition at steady-state levels within 2 hours[45, 46].

2.2.4 *Combination Clopidogrel-Aspirin*

Clopidogrel has been studied in combination with aspirin in several trials of vascular disease, including two that included patients with stroke or TIA. Although results from these trials have not supported long-term use of clopidogrel after stroke/TIA, the drug has never been tested as an acute therapy in this population and the trials support that it may be more beneficial and particularly safe after minor stroke or TIA.

Aspirin and clopidogrel synergistically antagonize platelet aggregation [44, 47- 49], and combined, may provide added benefit in stroke prevention. Aspirin and clopidogrel are used together after coronary, carotid, and intracranial stenting, and appear to be well tolerated [50, 51]. Evidence supporting clopidogrel also comes from cardiac trials, non-acute stroke/TIA trials, and most importantly, from an acute pilot trial of TIA and minor stroke, as reviewed below.

2.2.4.1 *Cardiac Trials*

The CURE trial of patients with acute coronary syndromes, also taking aspirin found that clopidogrel 75 mg/day after a loading dose of 300 mg reduced the risk of stroke, myocardial infarction, and vascular death by 20% at 3-12 month follow-up, and the effect was apparent in the first 10 days [52]. Myocardial infarction and vascular death accounted for the vast majority of events in this trial. There was a small increase in risk of major hemorrhage but no difference in life-threatening hemorrhage. In the CREDO study, clopidogrel also reduced the 1-year risk of cardiovascular events by 27% among those treated with aspirin undergoing percutaneous coronary intervention [53]. An early benefit was seen only in those who received a loading dose of clopidogrel 6 hours before the procedure, reinforcing the importance of an initial loading dose when ischemic events may occur within hours. There was a 1% absolute increase in risk of major bleeding at 28 days, but most of this was associated with procedures such as bypass surgery. Thus, clopidogrel reduces ischemic events in patients treated acutely after coronary ischemia or prior to percutaneous coronary intervention.

2.2.4.2 Non-Acute Stroke/TIA Trials

The MATCH (Management of atherothrombosis with clopidogrel in high-risk patients with

recent TIA or ischemic stroke) trial was a secondary stroke prevention trial that enrolled 7599 patients, mostly in Europe [54]. This study compared aspirin plus clopidogrel to clopidogrel. The majority of patients (79%) enrolled suffered a prior stroke, rather than TIA. The overall trial was negative, with a small insignificant 1% absolute benefit in terms of reduced risk of ischemic events balanced by a 1% but significant absolute increased risk of major hemorrhage. In subgroup analysis, however, there was a trend toward greater benefit in those treated sooner after the qualifying stroke or TIA, with a 17% RRR in those treated within 7 days. The CHARISMA trial randomized patients with vascular disease, who are treated with aspirin 75-162 mg/day, to clopidogrel 75 mg or placebo [55]. Similar to MATCH, the trial was negative with a small reduction in ischemic events balanced with a small significant increase in severe hemorrhages. However, also similar to MATCH, there was greater benefit in patients treated sooner after a clinical qualifying event (including stroke and TIA). In unpublished analysis of the 4320 patients enrolled in CHARISMA after TIA or stroke, a study involving Drs. Johnston and Easton (reviewed here to maintain continuity), the RRR of stroke with clopidogrel was 26% in those randomized within 30 days of the event and 17% in those randomized later, again suggesting that patients treated early are more likely to benefit. There was no increased risk of hemorrhage in those treated within 30 days or later among those randomized after stroke or TIA.

2.2.4.3 Pilot Acute TIA/Stroke Trials

FASTER [56] was a pilot trial evaluated clopidogrel (300 mg load and 75 mg/day afterwards) and simvastatin in a factorial design on a background of aspirin in patients presenting within 24 hours of a TIA or minor stroke. The main principal motivating the trial was the recognition of the high frequency of poor outcomes in patients presenting with acute cerebral ischemia who are not candidates for thrombolysis. The trial enrolled 392 patients from 18 centers over 30 months. The risk of stroke (ischemic or hemorrhagic) at 90 days was 11% in those treated with aspirin alone and 7% in those treated with clopidogrel and aspirin, a non-significant 36% RRR in this pilot trial (p=0.19). There were two intracranial hemorrhages, both in patients treated with clopidogrel-aspirin; one occurred in a patient with minor stroke and uncontrolled blood

pressure and the other occurred in a patient with TIA but details are uncertain. These hemorrhages were included in the primary outcome and did not overwhelm the benefit. The trial serves as an excellent pilot for the proposed trial, reconfirming a high risk of stroke in patients with TIA and minor stroke and suggesting that a large effect size is possible.

Another pilot double-blind, placebo-controlled trial, CARESS, evaluated the impact of clopidogrel-aspirin vs. aspirin alone on presence of TCD micro-embolic signals in 107 patients with recently symptomatic carotid stenosis [57]. At 7 days, 44% on the combination and 73% on aspirin alone had persistent micro-embolic signals (p=0.005), suggestive of a reduction in ongoing thrombo-embolism. There were more strokes and TIAs in the aspirin-only group (11 vs. 4) but the difference was not significant.

2.2.4.4 Risks of major hemorrhage

Although the trials in non-acute stroke or TIA suggest that the combination increases risk of major hemorrhage, the risk of thrombosis is extremely high in the acute period after TIA or minor stroke and risk of hemorrhage is expected to be lower than after moderate or severe stroke, so the combination may be particularly effective and relatively safe in this setting. In fact, patients with TIA or minor stroke have minimal or no infarction, so their risk of hemorrhage may be more similar to those with cardiac disease than to those with completed strokes that are disabling enough to meet entry criteria in prior trial [58]. For example, in the TOAST study, risk of serious brain bleeding with danaparoid was 14% in those with an NIH Stroke Scale score >15 and only 0.5% in those with less severe stroke [59]. Thus, hemorrhage risk with the combination of aspirin and clopidogrel should be relatively low after TIA or minor stroke.

2.3 Conclusion

TIA or minor stroke is a neglected condition. Many studies have shown that the risk of stroke is higher than completed stroke in short-term. Effective therapies in those patients could significantly reduce the overall burden of stroke if initiated immediately. Antiplatelet therapy may play a distinct role in this acute pathophysiology. However, no large-scale trial has evaluated an acute intervention in patients with TIA or minor stroke.

The FASTER pilot trial, as well as other negative trials of clopidogrel in combination with ASA after stroke or TIA suggests that treatment with the combination might be beneficial when taken soon after a TIA or minor stroke. Of course, these data are only suggestive, because they are derived from small pilot studies and subgroup analyses, and they should not be taken as proof of clinical utility, but they do provide strong supports for a large-scale clinical trial to test the aggressive antiplatelet therapy in acute minor stroke or TIA [60]. In conclusion, taking all these data into account and given the high risk of vascular events after TIA or minor stroke, especially in acute setting, it anticipated that the proposed study design can maximize the benefit while minimizing the risk of bleeding events.

3 STUDY OBJECTIVES

3.1 Primary

The primary objective of this randomized, double-blind, multicenter clinical trial is to assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 30 Days versus a 3-month regimen of aspirin 75 mg/day alone on reducing the 3-month risk of **any new stroke (ischemic or hemorrhagic)** when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.

3.2 Secondary

3.2.1. To assess the secondary composite outcome: composite of any stroke, myocardial infarction, and vascular death.

3.2.2. To assess the primary outcome measure in a Per-protocol (PP) population. This will include all patients who have not had a significant interruption of study drug (Actual number doses taken less than 80% of expected number of doses taken) or major protocol violation.

3.2.3. To assess separately the effects of this Clopidogrel regimen versus ASA alone on the incidence of: new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) as a cluster and evaluated individually.

3.2.4. To evaluate change in modified Rankin Scale [mRS,(continuous)] and percentage with score 0-2 at last follow-up.

3.2.5. To compare the safety of the two treatment regimens in terms of:

- ✧ Severe or moderate bleeding (GUSTO definition, see appendix)
- ✧ Intracranial hemorrhage
- ✧ Total mortality
- ✧ AEs/SAEs
  - Thrombotic thrombocytopenic purpura (TTP)
  - Granulocytopenia
  - Hypersensitivity
  - Renal failure

3.2.6. To compare efficacy and safety by etiology, non-Intracranial artery diseases (non-ICAD) vs. ICAD (substudy)

3.2.7. To compare efficacy and safety by qualifying event, TIA vs. minor stroke.

3.2.8. To compare efficacy and safety in those previously taking ASA or Clopidogrel at presentation or not.

3.2.9. To compare efficacy and safety by gender and age (<65 years vs≥65 years).

3.2.10. In further exploratory analysis, to evaluate impairment (change in NIHSS scores), and Quality of Life (EuroQol EQ-5D scale) among survivors.

4 STUDY DESIGN AND MANAGEMENT OVERVIEW

4.1 Study Design Overview

The primary null hypothesis of this randomized, double-blind multicenter clinical trial is, there

is no difference in 90-day risk of any new stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 30 Days versus a 3-month regimen of aspirin 75 mg/day alone when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.

Patients with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (defined as an NIHSS ≤ 3), who can be treated within 24 hours of symptom onset will be enrolled. Patients meeting these criteria and offering informed content will be randomized into two groups: the first group will receive a 300mg loading dose of clopidogrel on the day of randomization, followed by 75 mg clopidogrel/day from Day 2 to 3 months. Aspirin will be given in a total dose ranging between 75 mg and 300 mg (open label with dose determined by the treating physician) on the first day, followed by blinded 75 mg once /day from Day 2 to 30. Between day 31 and 3-month visits, aspirin 75 mg will be replaced by a placebo of aspirin 75 mg. The second group will receive open label aspirin in a total dose ranging between 75 mg and 300 mg on the first day, followed by 75 mg once/day from Day 2 to 3 months. A placebo for clopidogrel will be given from the day of randomization until the 3-month visit. Subjects will be followed for 90 days and risk of any stroke (ischemic or hemorrhage) will be assessed in the treatment groups. The trial will be completed in 35 months, with 3,800 subjects recruited from about 80 centers in China in partnership with research network and CHANCE Clinical Research Collaboration. A Data and Safety Monitoring Board (DSMB) will regularly monitor safety during the study.

4.2 Study Milestones

A 3-year budget and recruitment plan have been created; key study milestones below.

STUDY MILESTONES

Pre-enrollment Study Initiation 9 months (2009.01-2009.09)

Recruitment and Follow-up	19 months (2009.10- 2011.04)
Completion of Follow-up	3 months (2011.05-2011.07)
Data Analysis and Publication	4 months (2011.08-2011.11)
Total Duration	35 months

4.3 Study Organization

Principal Investigator：

Yongjun Wang, Beijing Tiantan Hospital, Beijing, China；

S. Claiborne Johnston, University of California, San Francisco, USA

The Steering committee members of CHANCE study are as follows:

Pr. Yongjun Wang (PI)

Pr. Claiborne Johnston (USA- Co PI)

Pr. L. Wong (Hong Kong)

Pr. David Wang (USA)

Pr. James Wang (USA)

Pr. Mai N. Nguyen-Huynh (USA)

Pr. Liying Cui

Pr. Yansheng Li

Pr. Qiang Dong

Pr. JianfengXu

Pr. JianpingJia

Pr. Jiang Wu

Pr. JinshengZeng

Pr. Xingquan Zhao

Pr. Liping Liu

Pr. Chunxue Wang

Pr. Yilong Wang

The steering committee will provide scientific and strategic direction for the trial and will have overall responsibility for its design, execution, and publication.

The steering committee will also be responsible for ensuring that study execution and management are of the highest quality.

It will approve the protocol and the operational guidelines of the trial prior to its commencement.

The steering committee will convene regularly by teleconference or face-to-face meetings to discuss and report on the progress of the study.

The composition of the steering committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

Executive committee

The two co-chairs and additional members of the Steering Committee, including two project directors, will be members of the Executive Committee. They will convene more frequently (teleconferences or physical meetings) to review the status of the trial and available blinded data and will take appropriate actions regarding the conduct of the study.

A face-to-face Executive Committee meeting will be organized to make major decisions.

The composition of the Executive Committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

Data safety and monitoring board (DSMB)

The DSMB will meet regularly and monitor the progress of the CHANCE study to ensure that the study meets the highest standards of ethics and patient safety. It is composed of

Academic Members, including an independent statistician, who are not otherwise participating in the trial. A DSMB charter including membership role and responsibilities will be approved by both the DSMB and the Executive Committee before the start of the trial.

Written recommendations and their rationale will be provided to the Chairs of the Steering Committee immediately after each DSMB meeting.

DSMB members: Hao Li, Yilong Wang, Yong Zhou.

Adjudication committee

Clinical outcome events (stroke, MI, death, overt bleedings) will be reviewed by independent experts (neurologists, cardiologists). An adjudication committee charter including membership, role and responsibilities will be approved before the start of the trial by the Adjudication Committee and the Executive Committee.

Neuroimaging associated with clinical events will be read locally and reports will be included in adjudication packets. The adjudication committee may request actual images from sites or from the core lab in special instances.

Adjudication committee member: Yansheng Li, Anding Xu, Peiyi Gao

4.4 Site Training, Certification, and Update

Executive committee have already provided training to their sites in Good Clinical Practice Guidelines and in some outcome assessments (e.g., NIHSS, mRS).

Prior to initiation of patient enrollment, Site Investigators and Coordinators will complete training programs and their certifications. In these training modules, the patient selection criteria and follow-up procedures will be reviewed. Case studies illustrating potential problems in adhering to study protocol and blinding will be discussed.

All investigators must complete the following training modules, and receive certification:

- Study procedures
- Primer on the diagnosis of TIA and its mimics

- Use of the ABCD^2 score
- CHANCE eligibility
- Modified Rankin Scale
- NIHSS
- SSS-TOAST
- EQ-5D
- Outcome events adjudication
- GUSTO
- Collecting blood sample only for subgroup
- Collecting DICOM imaging data only for subgroup

Successful completion of the training program will be required before a site is certified to enroll patients. Telephone-based meetings, with the PI and key staff available to address questions, will occur intermittently. Certification of competence will be obtainable on the four training centers.

A detailed Manual of Procedures will serve as the primary document describing all study related procedures. It will serve as a guide for training of clinical center personnel and will be updated periodically throughout the study on the CHANCE website, as needed. A system composed of members of executive committee and clinical research associate will be implemented for the clinical centers to call, fax, or e-mail any procedural questions regarding the study. The CHANCE executive committee will formulate answers in consultation with the Steering Committee, and will periodically distribute to the participating centers a set of frequently asked questions (FAQ) and answers. These questions and answers will be available on the study website.

The members of executive committee will manage and conduct site visits for its sites and ensure the integrity and validity of the data recorded on the Case Report Forms. Each site will be visited at least once during the trial, and as needed if questions about data quality or

problems with recruitment arise.

4.5 Contact Schedule and Measurements

Subject encounters will include screening, randomization, hospital discharge, 30th day visit, and 90th day visit or a final event visit. In addition, event visits are to occur whenever patient contact suggests that a patient experiences a potential clinical neurological event, including a clinical deterioration that could be possibly related to ischemia, or new transient or persistent neurological symptoms, an adjudication packet will be produced by the site within 72 hours.

4.6 Outcomes

The definitions of endpoint outcomes are given in Appendix 1.

4.6.1 Primary Efficacy Endpoint

Percentage of patients with the 3-month new vascular events, defined as any event of the following:

- ✧ *Any stroke (ischemic or hemorrhagic)*

4.6.2 Secondary Efficacy Endpoint

- Percentage of composite of any stroke, myocardial infarction, and vascular death within 3 month.
- Patients with the 3-month new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) evaluated individually.
- Modified Rankin Scale score changes (continuous) and dichotomized at percentage with score 0-2 vs. 3-6 at 3 month follow-up (Scale is described in Appendix 2).
- Further efficacy exploratory analysis:
  - ✧ Impairment (changes in NIHSS scores at 3 month follow-up), (Scale is described in Appendix 3).

- ✧ Quality of Life (EuroQol EQ-5D scale, described in Appendix 4).

- Efficacy endpoint will also be analyzed stratified by etiological subtypes (non-ICAD vs. ICAD), by qualifying event (TIA vs. minor stroke), and by age (<65 years vs≥65 years).

4.6.3 Safety Endpoint

4.6.3 .1 Clinical Safety

Clinical safety will be assessed by:

- ✧ A physical examination including neurological evaluation at D1, hospital discharge, Ml and M3 visits.
- ✧ Adverse event collection at each visit after baseline
- ✧ Measurement of supine blood pressure and heart rate at each visit.

4.6.3 .2 Adverse Event Collection

No specific laboratory safety tests are required during this study. However, if a laboratory abnormality is clinically relevant or leads to an adverse event report, specific appropriate actions may be required (see Appendix 5, decision charts).

4.6.3 .3 Electrocardiogram

An ECG will be performed at the baseline visit (Day 1).

4.6.3 .4 Safety Endpoint

4.6.3.4.1 Primary safety endpoints

- ✧ Incidence of severe bleeding or moderate bleeding (GUSTO definition, see appendix 6), including fatal bleeding and symptomatic intracranial hemorrhage

4.6.3.4.1 Secondary safety endpoints

- ✧ Incidence of symptomatic and asymptomatic intracranial hemorrhagic events at 3 months
- ✧ Total mortality

- ✧ AEs/SAEs reported by the investigators

5 PARTICIPANT SELECTION

During the course of the trial, about 80 sites will enroll 3,800 subjects with TIA or minor ischemic stroke. Before enrolling patients into the study, all collaborating sites will obtain approval from local Institutional Review Boards (IRBs), which will have access to all study documentation and educational materials.

5.1 Study Population

Inclusion Criteria

- Adult subjects (male or female ≥ 40 years)
- Acute non-disabling ischemic stroke (NIHSS≤3 at the time of randomization) that can be treated with study drug within 24 hours of symptoms onset. Symptom onset is defined by the "last see normal" principle.
- TIA (Neurological deficit attributed to focal brain ischemia, with resolution of the deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate-to-high risk of stroke recurrence (ABCD2 score ≥ 4 at the time of randomization). Symptom onset is defined by the "last see normal" principle.
- Informed consent signed

Exclusion Criteria

- Diagnosis of hemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major non-ischemic brain disease (e.g., multiple sclerosis) on baseline head CT or MRI.
- Isolated or pure sensory symptoms (e.g., numbness), isolated visual changes, or isolated dizziness/vertigo without evidence of acute infarction on baseline head CT or

MRI.

- Modified Rankin Scale Score > 2 at randomization (pre-morbid historical assessment)
- NIH Stroke Score ≥ 4 at randomization
- Clear indication for anticoagulation (presumed cardiac source of embolus, e.g., atrial fibrillation, prosthetic cardiac valves known or suspected endocarditis).
- Contraindication to clopidogrel or ASA.
    - Known allergy
    - Severe renal or hepatic insufficiency
    - Severe cardiac failure, asthma
    - Hemostatic disorder or systemic bleeding
    - History of hemostatic disorder or systemic bleeding
    - History of thrombocytopenia or neutropenia
    - History of drug-induced hematologic or hepatic abnormalities
    - Low white blood cell (<2 x109/l) or platelet count (<100 x109/l).
    - Use of thrombolysis within 24 hours prior to randomization
- History of intracranial hemorrhage.
- Anticipated requirement for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function.
- Current treatment (last dose given within 10 days before randomization) with heparin therapy or oral anti coagulation.
- Gastrointestinal bleed or major surgery within 3 months.
- Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months (if clinically indicated, vascular imaging should be performed prior to randomization whenever possible)

- Scheduled for surgery or interventional treatment requiring study drug cessation.
- Qualifying TIA or minor stroke induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy < 3 months.
- Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- Currently receiving an investigational drug or device.

6 TREATMENTS

6.1 Study Drugs

This randomized double-blind study is primarily designed to compare a clopidogrel/aspirin combination versus an aspirin alone regimen. The two types of study tablets (75 mg active clopidogrel and placebo) are indistinguishable, identical in size, shape, color, appearance, and taste.

Minor side effects are unusual with the medication, so it is not anticipated that either subjects or clinicians will be able to differentiate the placebo from the active drug. Standard laboratory tests cannot detect the effects of clopidogrel.

Investigators will not have access to the randomization (treatment) code, except in exceptional circumstances, such as occurrence of a serious adverse event for which knowledge of the study medication would be considered essential for treating the subject.

6.2 Formulations

- ✧ Clopidogrel 75 mg tablets
- ✧ Placebo tablets of Clopidogrel 75 mg
- ✧ ASA 75 mg tablets
- ✧ Placebo tablets of ASA 75 mg

6.3 Route of administration

- ✧ Oral

6.4 Dose regimen

Group 1:

- ✧ Day 1*: four tablets of clopidogrel 75 mg and open label ASA (75 mg -300 mg)
- ✧ From D2 to D30±7 days: one tablets of clopidogrel 75mg and one tablet of ASA 75 mg per day
- ✧ From D31±7 days visit to D90±7 days(does not exceed 72 days between D31±7 days visit to D90±7 days): one tablets of clopidogrel 75mg and one tablet of placebo ASA 75 mg per day

* On Day1, patients will receive open label ASA (between 75-300 mg) with dose at the discretion of the investigator. This represents the total dose given on D1 (between 75-300 mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day.

Group 2:

- ✧ Day 1*: four tablets of placebo clopidogrel 75 mg and open label ASA (75 mg -300 mg)
- ✧ From D2 to D30±7 days: one tablets of placebo clopidogrel 75mg and one tablet of ASA 75 mg per day
- ✧ From D31±7 days visit to D90±7 days (does not exceed 72 days between D31±7 days visit to D90±7 days): one tablets placebo of clopidogrel 75mg and one tablet of ASA 75 mg per day.

*On Day1, patients will receive open label ASA (between 75-300 mg) with dose at the discretion of the investigator. This represents the total dose given on D1 (between 75-300 mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day.

Study drug will be started **as soon as possible** after randomization (within one hour).

7 STUDY DRUG HANDLING

7.1 Supply and Storage

Sanofi-Aventis will supply the blinded investigational products (study drug and placebo) used in the study. All investigational drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individual, and under the conditions described on the labeling.

7.2 Packaging and Labeling

Each patient will be assigned a "patient kit" according to the randomization list.

According to the study periods and visits, each patient kit will consist of both the public box and the patient box that includes two boxes. Each box is composed of two parts as following:

Public box including the open-label aspirin (A_0)

Two wallets of the packaging for 1st day: the first one is 50mg* 12 pills *15 pieces; the other one is 25mg * 30 pills * 1 piece. ASA in public box is available to 30 patients.

Patient box including box 1 and box 2

Box 1 for period from Day 1 to Day 30 ± 7:

- ✧ 1 wallet of 4 clopidogrel 75 mg tablets for Day 1
- ✧ and 1 wallet of 36 clopidogrel 75 mg tablets and 36 ASA 75 mg tablets for Day 2 to Day 30 ± 7

OR

- ✧ 1 wallet of 4 placebo clopidogrel 75 mg tablets for Day 1
- ✧ and 1 wallet of 36 placebo clopidogrel 75 mg tablets and 36 ASA 75 mg tablets for Day 2 to Day 30 ± 7

Box 2 for period from Day 31 ± 7 to Day 90 ± 7 (does not exceed 72 days between $D_{31\pm 7}$ to

$D_{90\pm7}$):

- ✧ 2 wallets of 36 clopidogrel 75 mg tablets and 36 placebo ASA 75 mg tablets each.

  (total: 72 tablets of clopidogrel 75 mg and 72 tablets of placebo ASA 75 mg)

OR

- ✧ 2 wallets of 36 placebo clopidogrel 75 mg tablets and 36 ASA 75 mg tablets each

  (total: 72 tablets of placebo clopidogrel 75 mg and 72 tablets of ASA 75 mg)

The content of the labeling will be in accordance with the local regulatory specifications and requirements.

7.3 Responsibilities

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product will be responsible for ensuring that the Investigational Product used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All Investigational Product shall be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pel1aining documentation, labeling, expiry date, etc.) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply Investigational Product to a third party, allows the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

7.4 Concurrent Treatment

7.4.1 Prohibited Concomitant Treatments

Use of the following medications after randomization and during the study period represents a protocol violation. However, if there is a clinical need that justifies the added risk of these interventions in the setting of study drug use, they should be employed at the discretion of the treating physician

- ✧ Open-label ASA (with the exception of day 1, see Figure 1)
- ✧ NSAIDs, Cox1 and Cox2 inhibitors. If absolutely necessary, NSAIDs may be given for less than 5 days but not sooner than 8 days after randomization
- ✧ Open-label thienopyridines (ticlopidine, clopidogrel)
- ✧ Dipyridamole
- ✧ All heparins
- ✧ Oral anticoagulants
- ✧ GPIIbIIIa receptor antagonists
- ✧ Thrombolytics
- ✧ Vascular intervention (surgery and / or angioplasty of any vessel). If intervention is absolutely necessary within the three months period after randomization, study drug will be stopped 5 days prior to the intervention. Study treatment will then be restarted unless the patient needs to take open label clopidogrel or aspirin. In this case, study drug will be restarted only when treatment with open label antiplatelet therapy has been stopped.

7.4.2 Permitted Concurrent Treatments

Any drugs other than those listed above are permitted (including anti-hypertensive medications), if considered necessary for the patient, with a stable dose (when possible), at the discretion of the Investigator.

Any treatment which is ongoing before randomization and/or prescribed or changed during the study must be recorded in the CRF.

7.4.3 Treatment Accountability and Compliance

Compliance will be assessed by counting returned tablets at each visit.

The investigator (or delegates) will complete the appropriate page of the CRF or study drug inventory log form.

The date of study drug interruption must also be recorded.

7.5 Treatment Discontinuation

The investigational product (IP) should be continued whenever possible. If the IP is stopped, it should be determined if the discontinuation can be made temporarily; permanent IP discontinuation should be a last resort. Any IP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

7.5.1 Temporary treatment discontinuation with investigational product(s)

Re-initiation of treatment with the Investigational Product will be done under close and appropriate clinical/and or laboratory monitoring (see Appendix 5 Decision Charts) once the Investigator has considered according to his/her best medical judgment that the role of the Investigational Product(s) in the occurrence of the event concerned was unlikely and there is no other contraindication to continuing in the study.

All temporary treatment discontinuation (< 10 days) and the date of treatment re-initiation should be recorded by the Investigator on the appropriate CRF pages when considered to be confirmed

7.5.2 Definition treatment discontinuation with investigational product(s)

A patient should discontinue the study drug for any of the following reasons:

- ✓ Intercurrent condition that requires discontinuation of the study (e.g. lab abnormalities, Appendix 5).
- ✓ Positive serum pregnancy test or desire to become pregnant
- ✓ Contraception cessation

7.5.3 Handling of patients after definitive treatment discontinuation

Patients will be followed according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of an AE, whichever comes last

All withdrawals should be recorded by the Investigator on the appropriate CRF pages when considered to be confirmed

All patients who have discontinued the study drug prior to the last visit should have a complete end-of-study visit at three months.

For patients considered lost to follow-up, the CRF must be completed up to the last visit performed. The Investigator should make every effort to contact the patient and to identify the reason why he/she failed to attend the visit and to determine his/her health status

7.5.4 Consequence

Patients who have been withdrawn from the study cannot be included again in the study. Their patient number and treatment must not be re-used.

The investigator will call the IVRS to notify the treatment discontinuation and/or the patient's withdrawal.

Randomized patients will not be replaced.

7.5.5 Retrieval and/or destruction of treatments

A detailed log of returned Investigational Product will be established by the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the partially used or unused Investigational Product unless the Sponsor provides written authorization to the contrary.

A potential defect in the quality of Investigational Product may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

7.6 Blinding System and Emergency Unblinding Procedure

7.6.1 Description of blinding methods

This randomized double-blind study is primarily designed to compare a clopidogrel /ASA combination followed by clopidogrel alone regimen versus an ASA alone regimen.

The two types of clopidogrel tablets developed (75 mg active clopidogrel and placebo clopidogrel) are indistinguishable (identical in size, shape, color, appearance).

The two types of ASA tablets developed (75 mg active ASA and placebo ASA) are indistinguishable (identical in size, shape, color, appearance).

No locally- used biological test that could potentially unblind the treatment is planned in this study.

Investigators will not have access to the randomization (treatment) code, except in exceptional circumstances, such as occurrence of a serious adverse event for which knowledge of the study medication would be considered essential for treating the subject.

7.6.2 Method of assigning patients to a treatment group

The randomization code list will be generated centrally by a Contract Research Organization (CRO).

The patient kits will be packaged in accordance with this randomization code list. During the treatment period, the patient will receive study medication corresponding to either the clopidogrel / ASA group or the ASA group using a randomization ratio of 1:1.

Randomization will be stratified according to the time from symptoms onset to randomization (＜12 hours or ≥12 hours).

The treatment number will be allocated using a centralized treatment allocation system (Inter-voiceResponse System, IVRS) on D1 (baseline visit). Before randomizing a patient, the investigator will have to contact the IVRS and give some information (such as study number, patient date of birth and initials, study site, and time between symptom onset and randomization). A treatment number will then be given to the investigator, who will give the first box of the corresponding package to the patient.

7.6.3 Access to the randomization code during the study

In case of an Adverse Event, the code may be broken only in exceptional circumstances when knowledge of the Investigational Product is essential for treating the patient. If possible, contact should be made with the Monitoring Team before breaking the code.

If the physician at the investigational site believes unblinding is needed, he/she must call the IVRS 24-hour unblinding service. All the calls will be documented by the CRO.

If the blind is broken, the Investigator will document the date, time of day and reason for the code break. Study drug will not be resumed afterwards.

8 SAFETY

8.1 Adverse Events Monitoring

All events will be managed and reported in compliance with all applicable regulations and will be included in the final Clinical Study Report (CSR).

8.2 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Efficacy endpoints will not be considered as AEs except if, because of the course or severity or any other features of such events, the Investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- ✓ Results in death, or
- ✓ Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- ✓ Requires inpatient hospitalization or prolongation of existing hospitalization, or
- ✓ Results in persistent or significant disability/incapacity, or
- ✓ Is a congenital anomaly/birth defect, or
- ✓ Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

These should also usually be considered serious.

Note: Examples of such events 3re intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions or asymptomatic ALT increase ≥ 10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

8.3 Obligation of the investigator regarding safety reporting

8.3.1 Adverse Events

All Adverse Events regardless of seriousness or relationship to Investigational Product, spanning the time from the first visit planned in the Clinical Trial Protocol/signature of the informed consent (i.e., occurring during the washout period) to the last visit planned in the protocol, are to be recorded on the corresponding page(s) included in the Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the

Investigational Product.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

8.3.2 Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately:

SEND (within 1 working day, preferably by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and fax number appear on the Clinical Trial Protocol;

ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly noted on any copy of source documents provided to the Sponsor. For laboratory results, include the laboratory normal ranges;

Follow-up of any Serious Adverse Event that is fatal or life threatening should be provided within one additional calendar week.

8.3.3 Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients; notably, he should follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or stabilization of the patient's condition;

In the case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;

In the case of any Serious Adverse Event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered.

9 STUDY PROCEDURES

9.1 Day 1 visit = Screening, inclusion or baseline visit

9.1.1 Screening and Inclusion

Inclusion and exclusion criteria will be assessed, and:

$ABCD^2$ score for TIA patients and neurological evaluation (Modified Rankin Scale and NIHSS) will be performed for screening subjects

An electrocardiogram (ECG) will be performed (12-lead) to rule out atrial fibrillation. A head CT or MRI scan will be required to rule out hemorrhage, vascular malformation, tumor, or abscess. Since ECG and head imaging are recommended for all patients presenting with TIA and minor stroke, the study will not cover these costs.

A screening form will be completed for all patients in whom enrollment is considered. These screening forms will be useful in determining whether specific groups of patients are under-represented in the study and to confirm participation of sites.

The patient will receive complete information about the study, both orally and in writing.

Those meeting all inclusion criteria and no exclusion criteria (see Section 5) will be invited to participate. Consent will be obtained directly from the subject prior to enrollment. .

9.1.2 Baseline Evaluation

Baseline evaluation will include patient demographic information, symptoms of the index event, medications, past medical history, family history, cigarette and alcohol use, examination findings, pretreatment Rankin Score.

Laboratory tests will be performed (serum creatinine, glycemia, neutrophil count (or at least a total WBC count) and platelet count)

A physical examination will be performed, including measurement of weight (kg) and vital signs (supine systolic and diastolic blood pressure, heart rate)

Results of head imaging, CBC, and ECG will be recorded using standardized instruments. .

9.1.3 Randomization

The statistician will develop a master randomization list, with stratification blocked to assure an equal distribution of treatments at each participating site. If the subject was confirmed, the investigator will call the IVRS for randomization and treatment group allocation. This system will allow Clinical Sites to perform participant enrollment around the clock, 7 days a week. A study number will correspond to a specific medication packet. This identifying number will be coded on the enrollment confirmation.

9.1.4 Treatment on DAY 1

The patient will receive Day 1 study medication and be instructed how to take the study medication. Time of first study drug administration will be recorded.

Study drug will be started as soon as possible after randomization (within 24 hours after onset).

ASA will be given at the discretion of the investigator, at a total dose for Day 1 between 75 and 300 mg.

The following information will be collected for each patient:

- ✓ Demographic (age, sex, ethnic origin)
- ✓ Patient's medical history and concomitant diseases
- ✓ Concomitant medications
- ✓ An appointment will be made for next study visit (D21 ± 2 days after randomization)

9.2 Hospital discharge Visit

During this visit:

- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)

- ✓ A physical examination will be performed, including measurement of weight (kg) and vital signs (supine systolic and diastolic blood pressure, heart rate)
- ✓ Information will be collected on concomitant medications and adverse events since the last visit
- ✓ Drug accountability and assessment of treatment compliance since Day 2 will be performed.
- ✓ Study medication (Day 2 to Day 30±7 wallet from Box 1) will be given back to the patient for home administration of study medication. Patient will be instructed how to take the study drug from hospital discharge day until the next visit
- ✓ An appointment will be made for next study visit (one month ± **7 days** after randomization)

9.3 Day 30 Visit = D 30±7

During this visit:

- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)
- ✓ A physical examination will be performed, including measurement of weight (kg) and vital signs (supine systolic and diastolic blood pressure, heart rate)
- ✓ Information will be collected on concomitant medications and adverse events since the last visit
- ✓ Treatment Box 1 with unused study medication from completed study period (with Day 1 and Day 2 to Day 30±7 wallets) will be collected for drug accountability and assessment of treatment compliance
- ✓ Treatment Box 2 (from Day 31±7 visit to Day 90±7 visit and does not exceed 72 days from $D_{31\pm7}$ to $D_{90\pm7}$) will be dispensed to the patient and he will be instructed how to take the study drug until next visit

- ✓ An appointment will be made for next study visit (three months **± 7 days** after randomization)

9.4 Three month Visit = D 90±7

Note: Number of days between M1 and M3 visits may not exceed 72 days.

During this visit:

- ✓ If the patient will be diagnosed by sICAD, MRI+MRA (MRI including T1 + T2 + DWI + FlAIR + T2*) sequences will be strongly encouraged to perform. Images will be transferred to the core imaging evaluation lab.
- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)
- ✓ Quality of life scale (EQ-5D) will be performed in a quiet room (Appendix 4)
- ✓ A physical examination will be performed, including vital signs (supine systolic and diastolic blood pressure, heart rate)
- ✓ Information will be collected on concomitant medications and adverse events since the last visit
- ✓ The treatment box from completed study period with unused study medication will be collected for drug accountability and assessment of treatment compliance

9.5 Possible event visit

If a patient experiences a potential clinical neurological event, including a clinical deterioration that could be possibly related to ischemia, or new transient or persistent neurological symptoms, an adjudication packet will be produced by the site within 72 hours. This will include the following:

- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)
- ✓ A physical examination will be performed, including measurement of weight (kg) and vital signs (supine systolic and diastolic blood pressure, heart rate)

- ✓ **If the patient will be diagnosed by sICAD, MRI (including T1 + T2 + DWI + FlAIR + T2*) sequences will be strongly encouraged to perform. Images will be transferred to the core imaging evaluation lab.**
- ✓ If a patient experiences a new potential cardiac event, a cardiac evaluation (including ECG) will be performed as clinically indicated. Information supporting a possible myocardial infarction will be collected in an adjudication packet and transmitted to the CRO within 72 hours.
- ✓ Information will be collected on concomitant medications and adverse events since the last visit.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis Plans

This section is an overview of the statistical considerations. Complete details can be found in the Statistical Analysis Plan (SAP). It provides the general specifications for the analysis of the data to be collected and presented in the Clinical Study Report. A final SAP will be issued prior to database lock and before code breaking. The SAP will define all "pre-specified, planned analyses."

10.1.1 Sample Size Estimates

10.1.1.1 Primary Null Hypothesis

In patients with TIA or minor ischemic stroke treated with aspirin 75 mg/day, there is no difference in 90-day risk of stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day compared to placebo when therapy is initiated within 24 hours of symptom onset.

The minimum necessary sample size in the trial is established by the requirement to detect the smallest expected, clinically meaningful treatment difference comparing the treatment

with placebo. A relative risk reduction of 22% (relative risk [RR] with addition of clopidogrel is 0.78) is the smallest difference we will attempt to detect.

With a sample size of 3800 patients, we will have 80% power to detect a relative risk reduction of 22% with a two-sided alpha of 0.05, and 5% drop outs (medication non-adherence) (Table 2 and Figure 2). The sample size formula used was based on the usual comparisons of proportions in two groups. This formula should provide more conservative estimates given that we plan a survival analysis for the trial.

Table 2. Sample size calculations for various risks (12% to 17%) of outcome in control (ASA) group

Power	n without drop outs	n with 5% drop outs	Risk of outcome in treatment group	Risk of outcome in control group	Relative risk with addition of clopidogrel
0.8	2880	3024	13%	17%	0.78
0.8	3094	3249	12%	16%	0.78
0.8	3334	3501	12%	15%	0.78
0.8	**3608**	**3788**	**11%**	**14%**	**0.78**
0.8	3926	4122	10%	13%	0.78
0.8	4296	4511	9%	12%	0.78
0.9	3856	4049	13%	17%	0.78
0.9	4140	4347	12%	16%	0.78
0.9	4462	4685	12%	15%	0.78
0.9	**4830**	**5072**	**11%**	**14%**	**0.78**
0.9	5254	5517	10%	13%	0.78
0.9	5750	6038	9%	12%	0.78

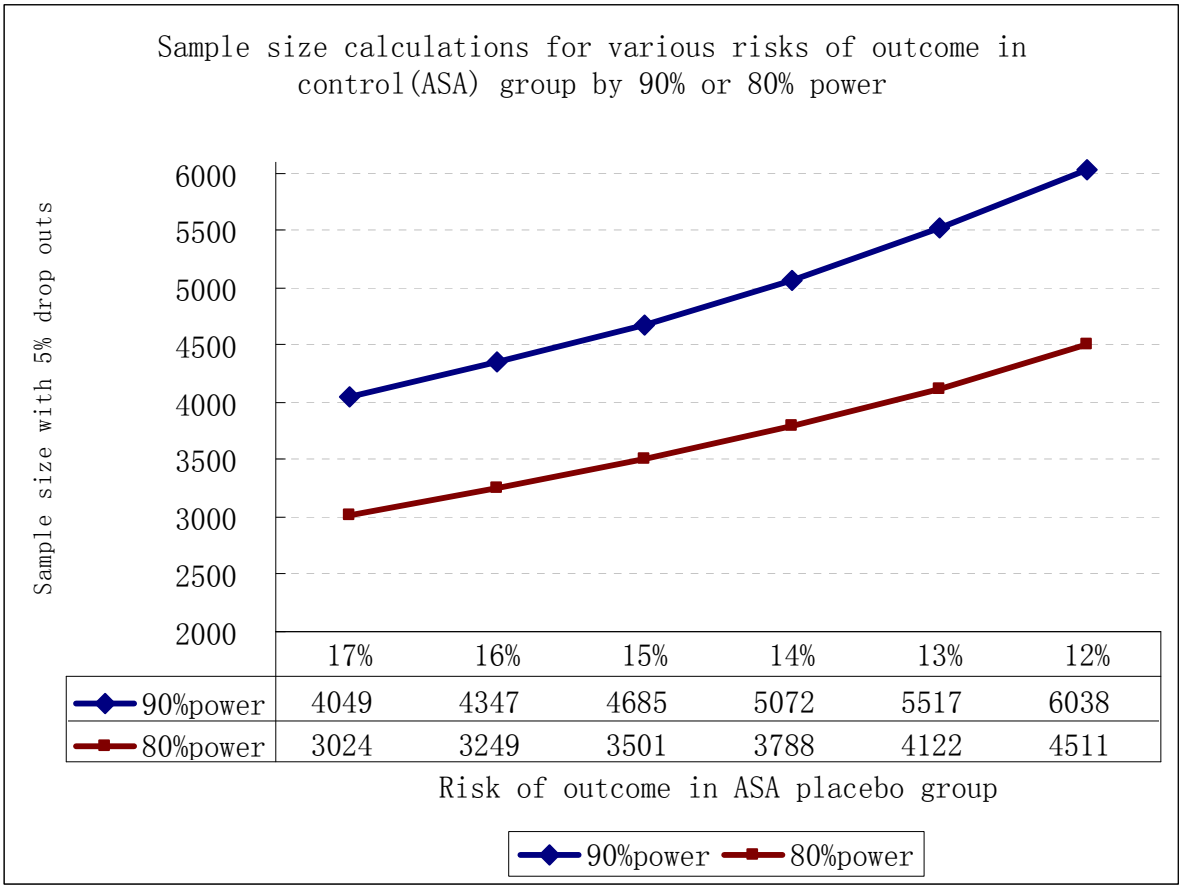


Figure 2. Sample size calculations for various risks of outcome in control (ASA) group by 90% or 80% power

10.1.1.1.1 Risk of outcome in placebo (ASA) group

Based on the pooled Northern California and Oxfordshire cohort study[62] and FASTER trial[56], the 90-day risk of the stroke recurrence risk in this group is about 14% among high-risk TIA (ABCD2 score > 4) or minor stroke patients treated with ASA within 24 hours of symptom onset.

Table 3. Risk estimation of outcome in placebo (ASA) group

Population	n	3-month Risks	
		Stroke	Stroke / MI / Death
All TIA[1]	2776	10.30%	12.14%

Excluding low-likelihood[1]	2325	11.87%	14.02%
ABCD[2] score in TIA[1]			
> 3	2067	12.58%	14.42%
> 4	1379	14.72%	16.75%
> 5	737	17.50%	19.94%
TIA and minor stroke [2]	194	10.8%	11.9%

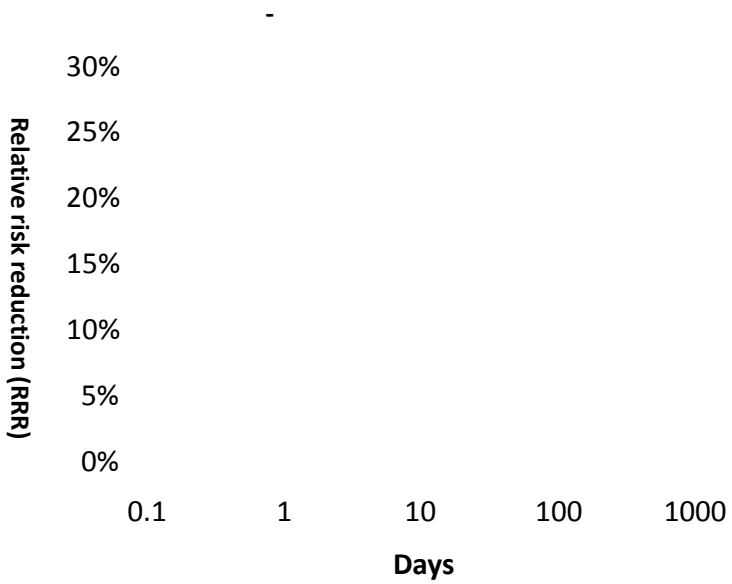
[1] Based on the pooled Northern California and Oxfordshire cohort study[62].

[2] FASTER trial[56].

10.1.1.1.2 Relative risk with addition of clopidogrel to ASA

We anticipate that clopidogrel will reduce risk of the composite outcome—stroke, myocardial infarction, and vascular death—independent of ASA. The relative risk reduction (RRR) of clopidogrel compared to placebo demonstrated in the FASTER pilot trial was 34.3% (for any stroke), but confidence intervals were broad given its small size. Other estimates of RRR can be obtained from subgroup analyses of trials with broader entry criteria, though these include subgroups (esp, stroke) that we don't anticipate will respond as well, and treat patients for long periods of time, when the risk of drug remains and benefit is likely lower. In the CHARISMA trial, patients with stroke/TIA treated with clopidogrel-ASA within 21 days of stroke or TIA had a 24% RRR compared to ASA alone. In the MATCH trial, a RRR of 17% was demonstrated in patients treated within 7 days of stroke or TIA for ASA-clopidogrel compared to clopidogrel alone. Given prior safety results, we do not anticipate excess intracerebral or life-threatening hemorrhage with clopidogrel in patients with TIA. Therefore, inclusion of intracerebral hemorrhage in the composite outcome is not expected to reduce the apparent benefit of clopidogrel. Based on these prior studies, we suspect the RRR will be greater than 22% (Figure 3).

Figure 3. Impact of clopidogrel-ASA vs. either alone based on timing of enrollment after clinical event (Outcome: stroke, MI, or vascular death)



10.1.1.1.3 Clinical significance of relative risk

Sample size is based on the desire to detect a 22% relative risk reduction. With this relative risk reduction, treatment of 32 patients with TIA or minor stroke (regardless of other risk factors) would be expected to result in one fewer stroke event over 3 months, based on the pilot study results. This effect is likely to be considered clinically important by treating physicians; this level of benefit is greater than that of ASA in secondary prevention after stroke, and ASA is widely accepted and utilized in this setting.

10.1.1.1.4 Delay between symptom onset and enrollment

Strokes may occur before randomization due to delays in enrollment. Patients with events occurring within 24 hours of TIA symptom onset were eliminated from the analysis of event rates since many of these patients would not have been enrolled and treated before the outcome occurred.

10.1.1.1.5 Losses to follow-up/non-adherence

These computations allow for a 5% rate of drop outs (medication non-adherence).

10.1.1.1.6 Power and alpha

Given the uncertainty in the assumptions used to predict effect size and event rates, we have chosen a sample size to provide 80% power (two-sided test, at the 5% difference level).

In summary, approximately 1900 patients per arm (3800 total) will give 80% power to detect a relative risk reduction of 22% with a two-sided alpha of 0.05, and 5% drop outs (medication non-adherence) (Table 2, Figure 2) 22% (relative risk [RR] with addition of clopidogrel is 0.78).

10.2 Statistical Analyses

A detailed statistical analysis plan will be created during the start-up period of the trial, which will include all tables and details of all analyses.

10.2.1 Primary Outcomes

The primary analysis will be intention to treat, with inclusion determined by receipt of first study drug dose. Missing values will remain missing and patients will be censored at their last follow-up assessment (time of clinical event, end of study, or last visit prior to loss to follow-up). Time to randomization was presented with group mean. Differences between treatments in the risk of stroke (ischemic or hemorrhagic) event during maximum 90-day follow-up were assessed using standard Kaplan-Meier time-to-event approaches, and the hazards ratios with 95% CI were reported. The time to the first event was used in the model when there were multiple events of the same type. This approach is being taken to maximize the time dependent information in the trial while still acknowledging the ease of interpretation of risks. All statistics will be two-sided with $p<0.05$ considered significant.

10.2.2 Secondary Outcomes

The analysis strategy outlined for the primary outcome will be used for most of the secondary analyses. For continuous outcomes (such as NIHSS and mRS), we will use a multiple linear regression analysis. Continuous outcomes will be checked for approximate normality and heteroscedasticity of residuals and for outliers. Transformations and/or weighted least squares will be considered as remedies for non-normality and heteroscedasticity. Outliers will be checked for validity and their influence on conclusions will be tested in sensitivity analyses.

11 ETHICAL AND REGULATORY STANDARDS

11.1 Ethical principles

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice.

11.2 Laws and regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, and Chinese laws and regulations in which the Clinical Trial is performed, as well as any applicable guidelines.

11.3 Informed consent

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

11.4 Institutional Review Board/Independent Ethics Committee(IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC)

composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form,

Investigator's Brochure, Investigator's CV, etc.), the list of voting members along with their qualification and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Clinical Trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

If requested, a progress report will be sent to the Ethics Committee (IRB/IEC) annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

12 STUDY MONOTORING

12.1 Responsibilities of the investigator(s)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical

Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. During these monitoring visits, the following, but not exhaustive, points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

12.2 Source document requirements

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre- identified

source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRS/IEC), and the regulatory authorities to have direct access to source data which support the data on the Case Report Forms (e.g., patient's medical file, appointment books, original laboratory records, etc.). Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

12.3 Use and completion of Case Report Forms(CRFS) and additional requests

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to the Sponsor's instructions) all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated.

The CRFs will be faxed (data fax system) visit per visit or collected at each routine monitoring visit.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests (ORF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the CRFs held by the Investigator and the Sponsor.

12.4 Use of computerized systems

Computerized systems will be used to create, modify, maintain, archive, retrieve and transmit data (IVRS, monitoring tool, data entry and statistical analysis).

13 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. The trial results will be published as soon as possible after database lockdown.

This trial will produce detailed data on treatment effects, medical care, and outcomes in a cohort of 3800 subjects with TIA or minor ischemic stroke. CHANCE biostatisticians will be consulted to assure that it is impossible to uniquely identify any participant. This may mean removing or categorizing certain variables. A data use agreement will not be required for access to this dataset. Diskettes with the data in comma-delimited text format will be sent to parties that express interest, including a data dictionary in a text file.

14 ANCILLARY STUDIES

Proposals for ancillary studies will be reviewed by the Executive Committee. Sites will not be required to participate in any ancillary study that requires additional data collection, but they will be encouraged to participate in accepted studies. Publication of the results of these studies will be governed by the policies and procedures developed by the Executive Committee.

15 REFERENCES

1. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH,Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. Lancet Neurol 2007;6(5):456-64.

2. Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. Circulation 2001;103(3):462-8.

3. Shi FL, Hart RG, Sherman DG,Tegeler CH. Stroke in the People's Republic of China. Stroke 1989;20(11):1581-5.

4. Brown RD Jr, Petty GW, O'Fallon WM, WiebersDO,Whisnant JP.Incidence of transient ischemic attack in Rochester, Minnesota, 1985-1989. Stroke 1998;29(10):2109-13.

5. Wolf, P.A. and L.A. Cupples. Incidence and prevalence of transient ischemic attack. In: W.S. Moore, ed. Surgery for Cerebrovascular Disease. New York:Churchill Livingstone,1987.

6. Edlow JA, Kim S, Pelletier AJ,Camargo CA Jr. National study on emergency department visits for transient ischemic attack, 1992-2001. AcadEmerg Med 2006;13(6):666-72.

7. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998;29(2):415-21.

8. Yi Long Wang, Di Wu, Xiaoling Liao, Wei Zhang, Xingquan Zhao, Yong Jun Wang.Burden of stroke in China. International Journal of Stroke 2007;2(3):211-213.

9. Wang W, Zhao D, Wu G, Liu J, Liu S, Qin L, et al. Trend analyses in the incidence of acute intracerebral hemorrhage events and acute cerebral infarction events in urban areas in Beijing. Zhonghua Liu Xing Bing XueZaZhi 2002;23(5):352-5.

10. Jiang B, Wang WZ, Chen H, Hong Z, Yang QD, Wu SP, et al. Incidence and trends of stroke and its subtypes in China: results from three large cities. Stroke 2006;37(1):63-8.

11. Zhao D, Liu J, Wang W, Zeng Z, Cheng J, Liu J, et al. Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project. Stroke

2008;39(6):1668-74.

12. Rothwell PM, Buchan A,Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. Lancet Neurol 2006;5(4):323-31.

13. Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Jimenez-Conde J, Pont-Sunyer C, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke 2008;39(6):1717-21.

14. Johnston SC, Gress DR, Browner WS,Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284(22):2901-6.

15. Coull AJ, Lovett JK,Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328(7435):326.

16. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36(4):720-3.

17. Gladstone DJ, Kapral MK, Fang J, LaupacisA,Tu JV. Management and outcomes of transient ischemic attacks in Ontario. CMAJ 2004;170(7):1099-104.

18. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, SvensonLW,Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62(11):2015-20.

19. Eliasziw M, Kennedy J, Hill MD, Buchan AM,Barnett HJ. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ 2004;170(7):1105-9.

20. Friedman GD, Wilson WS, Mosier JM, ColandreaMA,Nichaman MZ. Transient ischemic attacks in a community. JAMA 1969;210(8):1428-34.

21. Ueda K, Kiyohara Y, Hasuo Y, Yanai T, Kawano H, Wada J, et al. Transient cerebral ischemic attacks in a Japanese community, Hisayama, Japan. Stroke 1987;18(5):844-8.

22. Whisnant JP, Matsumoto N,Elveback LR. Transient cerebral ischemic attacks in a community. Rochester, Minnesota, 1955 through 1969. Mayo ClinProc 1973;48(3):194-8.

23. Dennis MS, Bamford JM, SandercockPA,Warlow CP. A comparison of risk factors and prognosis for transient ischemic attacks and minor ischemic strokes.TheOxfordshire Community Stroke Project. Stroke 1989;20(11):1494-9.

24. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333(24):1581-7.

25. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. Neurology 2005;64(4):654-9.

26. Weinberger J. Antiplatelet agents for stroke prevention following transient ischemic attack. South Med J 2008;101(1):70-8.

27. Emre U, RantanenK,Tatlisumak T. Antithrombotic treatment in the prevention of ischemic stroke. Curr Drug Targets 2007;8(7):817-23.

28. Albers GW. Antithrombotic therapy for prevention and treatment of ischemic stroke. J Thromb Thrombolysis 2001;12(1):19-22.

29. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349(9066):1641-9.

30. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349(9065):1569-81.

31. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31(6):1240-9.

32. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38(5):1655-711.

33. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA, et al. National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol 2006;60(3):301-13.

34. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39(5):1647-52.

35. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37(2):577-617.

36. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25(5):457-507.

37. Halkes PH, van Gijn J, Kappelle LJ, KoudstaalPJ,Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006;367(9523):1665-73.

38. Diener HC, Cunha L, Forbes C, Sivenius J, SmetsP,Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J NeurolSci 1996;143(1-2):1-13.

39. Diener HC, Sacco R,Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). Cerebrovasc Dis 2007;23(5-6):368-80.

40. Ralph L. Sacco, on behalf of the PRoFESS Study Group. Prevention Regimen For Effectively avoiding Second Strokes - The PRoFESS Trial Results. Presented at European Stroke Conference 2008.

41. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. Drugs 2007;67(4):613-46.

42. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. Drugs 2000;60(2):347-77.

43. Sharis PJ, Cannon CP,Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. Ann Intern Med 1998;129(5):394-405.

44. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348(9038):1329-39.

45. Helft G, Osende JI, Worthley SG, Zaman AG, Rodriguez OJ, Lev EI, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. ArteriosclerThrombVascBiol 2000;20(10):2316-21.

46. Savcic M, Hauert J, Bachmann F, Wyld PJ, GeudelinB,Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. SeminThrombHemost 1999;25Suppl 2:15-9.

47. Herbert JM, Dol F, Bernat A, Falotico R, LaleA,Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. ThrombHaemost 1998;80(3):512-8.

48. Harker LA, Marzec UM, Kelly AB, Chronos NR, Sundell IB, Hanson SR, et al. Clopidogrel

inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. Circulation 1998;98(22):2461-9.

49. Makkar RR, Eigler NL, Kaul S, Frimerman A, Nakamura M, Shah PK, et al. Effects of clopidogrel, aspirin and combined therapy in a porcine ex vivo model of high-shear induced stent thrombosis. Eur Heart J 1998;19(10):1538-46.

50. Jauhar R, Bergman G, Savino S, Deutsch E, Shaknovich A, Parikh M, et al. Effectiveness of aspirin and clopidogrel combination therapy in coronary stenting. Am J Cardiol 1999;84(6):726-8, A8.

51. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99(18):2364-6.

52. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, TognoniG,Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(7):494-502.

53. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288(19):2411-20.

54. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364(9431):331-7.

55. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354(16):1706-17.

56. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, DemchukAM,Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised

controlled pilot trial. Lancet Neurol 2007;6(11):961-9.

57. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111(17):2233-40.

58. Hart RG, Easton JD. Do we really need a better way to give heparin in acute cerebral ischemia?. Stroke 2002;33(3):659-60.

59. Adams HP Jr, Woolson RF, Clarke WR, Davis PH, Bendixen BH, Love BB, et al. Design of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Control Clin Trials 1997;18(4):358-77.

60. Johnston SC. Towards FASTER treatment of TIA and minor stroke. Lancet Neurol 2007;6(11):941-3.

61. Salthouse TA. The role of memory in the age decline in digit-symbol substitution performance. J Gerontol 1978;33(2):232-8.

62. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369(9558):283-92.

16 APPENDIXS

Appendix 1: Definition of End Points

Stroke	Sudden symptoms and signs of focal disturbance of cerebral function associated with cerebral circulation disorders. Etiology would be classified based on SSS-TOAST standard.
Ischemic stroke	An acute focal infarction of the brain or retina. Criteria: (1) acute onset of a new focal neurological deficit with clinical or imaging evidence of infarction lasting more than

	24 hours and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or (2) acute onset of a new focal neurological deficit and not attributable to a non-ischemic etiology lasting less than 24 hours, but accompanied by neuroimaging evidence of new brain infarction; or, (3) rapid worsening of an existing focal neurological deficit lasting more than 24 hours and not attributable to a non-ischemic etiology, and accompanied by new ischemic changes on brain MRI or CT, and clearly distinct from the index ischemic event.
Hemorrhagic stroke	An acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurological symptoms.
TIA	A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain. Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)
Symptomatic intracerebral hemorrhage	Any extravascular blood in the brain associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Intracerebral hemorrhage is defined as an acute extravasation of blood into the brain parenchyma. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy

Asymptomatic intracerebral hemorrhage	an acute extravasation of blood into the brain parenchyma without clinical deterioration. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy
Other symptomatic intracranial hemorrhage	Any extravascular blood within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Other Asymptomatic intracranial hemorrhage	An acute extravasation of blood into the subarachnoid space, epidural space, or subdural space without associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Myocardial infarction with coronary revascularization	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, treated with coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Myocardial infarction without coronary	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, not treated with

revascularization	coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Coronary Revascularization without myocardial infarction	A procedure to improve coronary blood flow for documented coronary artery disease, but with no documentation of myocardial infarction. Criteria: Documented coronary angioplasty, stenting, or bypass surgery for demonstrated or presumed coronary artery disease
Ischemic vascular death	Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause
Hemorrhagic Vascular death	Death due to intracranial or systemic hemorrhage

Appendix 2: modified Rankin Scale

The modified Rankin Scale (mRS) is a scale commonly used for measuring the degree of disability or dependence in the daily activities of individuals who have suffered a stroke, and it has become the most widely used clinical outcome measure for stroke clinical trials.

Description	**Score** (select one)
No symptoms at all	**0** ☐
No significant disability despite symptoms; able to carry out all usual duties	**1** ☐

and activities	
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	**2** ☐
Moderate disability; requiring some help, but able to walk without assistance	**3** ☐
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	**4** ☐
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	**5** ☐

Appendix 3: NIH Stroke Scale

Administer stroke scale items in the order listed. Record the performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	**Scale Definition**	**Score**
1a. Level of Consciousness: The investigator must choose a response 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, and flexic.	_____

Instructions	Scale Definition	Score
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 him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
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;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is 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. Patients may 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 respond to item 11.	**0 = No visual loss.** **1 = Partial hemianopia.** **2 = Complete hemianopia.** **3 = Bilateral hemianopia** (blind including cortical blindness).	_____

Instructions	Scale Definition	Score
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. 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 barriers obscure the face, these should be removed to the extent possible.	**0 = Normal**symmetrical movements. **1 = Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). **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. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 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, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	**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.** **UN** = Amputation or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____

Instructions	Scale Definition	Score
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls 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 leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	**0 = No drift;** leg holds 30-degree 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.** **UN** = Amputation or 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 of visual defect, ensure 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, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	**0 = Absent.** **1 = Present in one limb.** **2 = Present in two limbs.** **UN = Amputation or joint fusion**, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick 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 sensory loss," 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 brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically 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 of being touched. **2 = Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____

Instructions	Scale Definition	Score
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, 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 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 a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for 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.	**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 materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. **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 barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	**0 = Normal.** **1 = Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood with some difficulty. **2 = Severe dysarthria;** 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. **UN = Intubated** or other physical barrier, explain:_____ ___	_____

Instructions	Scale Definition	Score
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 extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	____
	Total NIHSS:	____

Appendix 4: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

☐I have no problems in walking about

☐I have no problems in walking about

☐I am confined to bed

Self-Care

☐I have no problem with self-care

☐I have some problems washing or dressing myself

☐I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure activities)

☐I have no problems with performing my usual activities

☐I have some problems with performing my usual activities

☐I am unable to perform my usual activities

Pain/discomfort

☐I have no pain or discomfort

☐I have moderate pain or discomfort

☐I have extreme pain or discomfort

Anxiety/depression

☐I am not anxious or depressed

☐I am moderately anxious or depressed

☐I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

how good or bad

your own health is today

Questionnaire completed by:

☐$_1$Patients independently

☐$_2$Patients with help of others

☐ $_3$Agent (the patient's family members)

Appendix 5: Abnormal clinical laboratory indicators

bleeding tendency	Prothrombin time >1.5 times control or platelet count<10×10^9/L
moderate or severe anemia	Hemoglobin (Hb)<90g/L
abnormal liver function	Transaminase beyond the normal more than two times
Abnormal renal function	Serum creatinine>1.5mg/dl or creatinine clearance rate<50ml/min

Appendix 6: GUSTO classification

Severe Bleeding	Documented intracranial hemorrhage or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention (other than vascular site repair), or CPR to maintain a sufficient cardiac output.
Moderate Bleeding	Bleeding that requires transfusion of blood but does not lead to hemodynamic compromise requiring intervention.
Mild Bleeding	Bleeding not requiring' transfusion and not causing hemodynamic compromise. This includes subcutaneous bleeding, mild hematomas, oozing from puncture sites, etc.

Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events(CHANCE)

Study Protocol

Supported by

The Ministry of Science and Technology of the People's Republic of China

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Protocol Version 1.4

July 25, 2009

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PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements.

I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, ICH Good Clinical Practices Guidelines and Institutional Review Board (IRB) requirements.

Clinical Site

_____ _____

Site Principal Investigator Signature Date

Site Principal Investigator Printed Name

CHANCE PROTOCOL SYNOPSIS

Title:	**C**lopidogrel and Aspirin versus Aspirin Alone for the Treatment of **H**igh-risk Patients with **A**cute **N**on-disabling **C**erebrovascular **E**vent (CHANCE): a Randomized, Double-blind, Placebo-controlled Multicenter Trial
Primary Objective:	To assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 21 Days versus a 3-month regimen of aspirin 75 mg/day alone on reducing the 3-month risk of any stroke (both ischemic and hemorrhagic) when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.
Study Design:	a randomized, double-blind, multicenter, placebo-controlled clinical trial with the primary null hypothesis that, there is no difference in 90-day risk of any new stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 21 Days versus a 3-month regimen of aspirin 75 mg/day alone when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke. .

Patient Population:

Patients 40 years of age or older with high-risk TIA (defined as an $ABCD^2$ score $\geq$ 4) or minor ischemic stroke (with NIHSS $\leq$3) who can be randomized and treated within 24 hours of symptom onset will be enrolled.

Inclusion/Exclusion Criteria:

Inclusion Criteria

- Adult subjects (male or female $\geq$ 40 years)
- Acute non-disabling ischemic stroke (NIHSS$\leq$3 at the time of randomization) that can be treated with study drug within 24 hours of symptoms onset. Symptom onset is defined by the "last see normal" principle.
- TIA (Neurological deficit attributed to focal brain ischemia, with resolution of the deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate-to-high risk of stroke recurrence (ABCD2 score $\geq$ 4 at the time of randomization). Symptom onset is defined by the "last see normal" principle.
- Informed consent signed

Exclusion Criteria

- Diagnosis of hemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major non-ischemic brain disease (e.g., multiple sclerosis) on baseline head CT or MRI.
- Isolated or pure sensory symptoms (e.g.,

numbness), isolated visual changes, or isolated dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI.

- modified Rankin Scale (mRS) Score > 2 at randomization (pre-morbid historical assessment)
- NIHSS≥ 4 at randomization
- Clear indication for anticoagulation (presumed cardiac source of embolus, e.g., atrial fibrillation, prosthetic cardiac valves known or suspected endocarditis).
- Contraindication to clopidogrel or aspirin.
  - Known allergy
  - Severe renal or hepatic insufficiency
  - Severe cardiac failure, asthma
  - Hemostatic disorder or systemic bleeding
  - History of hemostatic disorder or systemic bleeding
  - History of thrombocytopenia or neutropenia
  - History of drug-induced hematologic or hepatic abnormalities
  - Low white blood cell (<2 x109/l) or platelet count (<100 x109/l).
  - Use of thrombolysis within 24 hours prior to randomization
- History of intracranial hemorrhage.

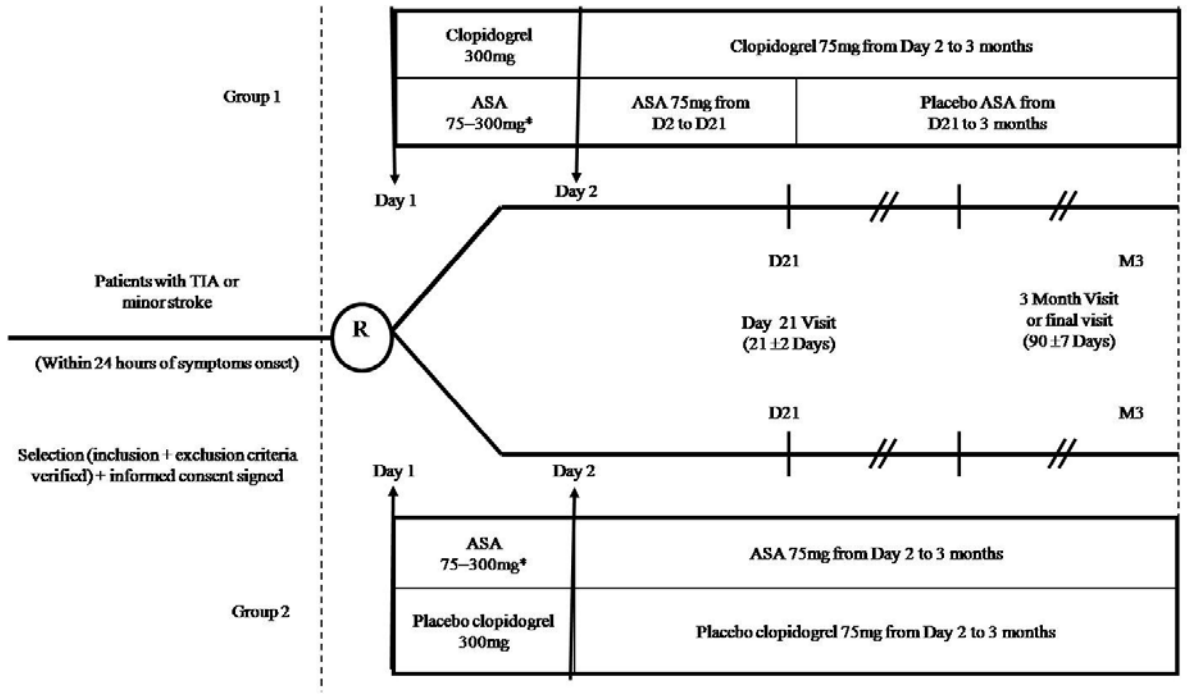
- Anticipated requirement for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function.
- Current treatment (last dose given within 10 days before randomization) with heparin therapy or oral anti coagulation.
- Gastrointestinal bleed or major surgery within 3 months.
- Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months (if clinically indicated, vascular imaging should be performed prior to randomization whenever possible)
- Scheduled for surgery or interventional treatment requiring study drug cessation.
- TIA or minor stroke induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy < 3 months.
- Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- Currently receiving an investigational drug or device.

Randomization:	The randomization code list will be generated centrally by a Contract Research Organization (CRO). The patient kits will be packaged in accordance with this randomization code list. During the treatment period, the patient will receive study medication corresponding to either the clopidogrel / ASA group or the ASA group using a randomization ratio of 1:1. The treatment number will be allocated using a centralized treatment allocation system (Inter-voiceResponse System, IVRS) on D1 (baseline visit). Before randomizing a patient, the investigator will have to contact the IVRS and give some information (such as study number, patient date of birth and initials, study site, and time between symptom onset and randomization). A treatment number will then be given to the investigator, who will give the first box of the corresponding package to the patient.
Primary Endpoint:	Percentage of patients with new stroke (ischemic or hemorrhage) at 3 months.
Study Duration for Each Subject:	Each subject is followed for 90 days from randomization; the trial will be completed in 3 years.
Number of Centers:	Up to a total of about 100investigational sites in the China in Clinical Research Network.

Sample Size:	Total sample size for the study is 5,100 subjects.
Primary Statistical Analysis:	The time to first new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period for the ITT Population will be summarized by treatment group using Kaplan-Meier estimates. The hazard ratio for the treatment comparison will be derived using a Cox's proportional hazards model, including the pooled study center as a random effect. The hazards ratios with 95% CI will be reported.

2 STUDY FLOWCHARTS

1.1 Graphical Study Design



*Open label ASA: at the discretion of the investigator. The represents the total dose given on D1 (between 75-300 mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day.

Flow Chart of CHANCE

1.2 Schedule of Activities and Assessments

Measurements	Screening Visit	Treatment Period			
		Randomization Day 1	21 days visit D21 ±2 days	Final Visit D90±7 days	Event Visit
Demographic Characteristics	x				
Modified Rankin Score	x		x	x	x
NIHSS	x		x	x	x
ABCD2 score (for TIA)	x				
Focused Medical History	x				
Current Medications	x		x	x	x
CT/MRI Scan	x*				
Laboratory tests**	x*				x
ECG	x*				x
Inclusion/Exclusion	x				
Informed Consent signed	x				
Randomization (IVRS)	x				
MRI Scan	x***			x***	x
Blood Sample		x****			
EuroQol (EQ-5D)				x	
1st treatment pack given		x			
2nd treatment pack given			x		

AEs/ SAEs			x	x	x
Treatment compliance			x	x	x

* Standard assessment: Expense not from research funding during baseline period

** Include: Blood routine test (including WBC count, Neutrophil count, Hemoglobin, platelet count, etc.), Blood coagulation, fasting plasma glucose, Hepatorenal function (including Creatine, Serum transaminase).

*** Include: T1+T2+DWI+MRA+Flair+T2*. MRI Scan needed only for subgroup would be completed before/after randomization according to the condition at centers.

****Blood sample needed only for subgroup would be collected as soon as possible after randomization.

2 BACKGROUND AND RATIONAL

2.1 The burden of acute non-disabling cerebrovascular event in China

China bears the biggest burden of cerebrovascular diseases in the world, not only because of its huge population but also the propensity for cerebrovascular diseases; the number of patients who die from cerebrovascular diseases is more than three times that from cardiovascular diseases [1, 2].

Acute non-disabling cerebrovascular event, including transient ischemic attack (TIA), defined as a mini-stroke that symptoms last less than 24 hours, and acute ischemic minor stroke, defined as an ischemic stroke with NIH Stroke Scale score ≤3, is common and often a precursor of a disabling stroke. Ischemic cerebrovascular event i.e. ischemic stroke (IS) and TIA became the predominant cerebrovascular diseases subtype, it was estimated that over 2 million new stroke events occurred each year in China [1, 3], and data from the China National Stroke Registry (CNSR), a national hospital-based registry across China showed that there were about 65% patients with ischemic stroke, and of these, more than 10% were minor ischemic stroke (unpublished data). So far it has not been reported about the incidence of TIA in China. The incidence of TIA in the United States (US) was approximately 68 per 100,000 to 86 per 100,000 person-years, corresponding to about 300,000 TIAs diagnosed each year [4- 7]. Based on the epidemiological studies in the US, it was estimated that at least 2million new TIA events would be diagnosed each year in China. What is more worrying about is that the incidence and mortality of stroke in the western country were declined yearly since the late 20th century, whereas ischemic stroke has been increasing annually and becomes the second leading cause of death in China.[2, 8- 11]

In addition, recurrence of stroke and other vascular events in patients with an initial acute nondisabling cerebrovascular event is one of the most frustrating medical situations.[12, 13] Several cohort studies have shown that early (3 months) risk of stroke following index transient ischemic attack (TIA) and minor ischemic stroke is much higher than previously

thought, even in patients treated with ASA, the current standard of care. [14- 18] Although comparisons across studies are limited by heterogeneity of study populations and clinical settings, they have shown a 90-day stroke risk of 10% to 20% after TIA or minor ischemic stroke.[14, 15, 18- 23]

2.2 Potential treatments of acute non-disabling cerebrovascular event

There are few established, effective therapies for stroke prevention after acute non-disabling cerebrovascular event. Other than ASA, the only approved drug for acute cerebral ischemic event is intravenous tissue plasminogen activator (tPA) [24]. However, for patients arriving within 3 hours of symtoms onset, the most common reasons for ineligibility for thrombolysis are that the deficit is improving or too mild to warrant treatment, and most patients arrive outside the narrow 3 hour window [25]. Thus, no acute therapy is available for the vast majority of patients with acute non-disabling cerebrovascular event.

Platelet aggregation is an important contributing factor in cerebral ischemia, as in other forms of ischemia. Antiplatelet agents reduce the risk of ischemic stroke in a variety of settings with distinct pathophysiologies (e.g., atrial fibrillation, small-vessel stroke, and large-vessel atherothrombosis) [26- 28].

2.2.1 ASA

ASA is the only anti-platelet agent to have been studied in patients presenting acutely with a cerebrovascular event, but the effect is modest and is reduced by a small increased risk of intracerebral hemorrhage. The CAST and IST studies, each enrolling about 20,000, found that acute treatment with aspirin after ischemic stroke reduced the risk of recurrent ischemic stroke by 30% (an absolute change of 0.7%) with a small increase in intracranial hemorrhage (25% relative and 0.2% absolute increase) over 2-4 weeks of treatment [29- 31]. Thus, aspirin has become the standard of care in the acute treatment of patients with stroke. The optimum dose of aspirin continues to be vigorously argued, but is probably in the range of 50-325 mg/day [32]. Aspirin is also considered standard therapy in TIA, with clopidogrel and aspirin-dipyridamole acceptable alternatives, but none has been tested as acute therapy in this setting. [33- 36]

2.2.2 Dipyridamole

Two trials have demonstrated the efficacy of dipyridamole in preventing stroke recurrence: ESPRIT [37] and ESPS-II [38]. Both tested dipyridamole combined with aspirin and found it superior to aspirin alone. In the ESPRIT trial, there was no increased risk of hemorrhage when dipyridamole was added to aspirin. Neither trial evaluated the acute period after a stroke or TIA (median time to enrollment was >21 days), so safety and efficacy during this time period is unknown.

The PROFESS trial [39, 40] failed to meet the pre-specified non-inferiority criteria for aspirin/extended-release dipyridamole vs. clopidogrel and aspirin/extended-release dipyridamole and clopidogrel had similar rates of recurrent stroke and major vascular events. Major hemorrhagic events, including intracranial bleeds, were more frequent among those treated with aspirin/extended-release dipyridamole, but the absolute risks were low and partially offset by fewer ischemic events. In China, aspirin/extended-release dipyridamole has not been currently approved by the Chinese SFDA, Combination of ASA and Clopidogrel is the exclusive options for the high-risk populations or in the acute setting.

2.2.3 Clopidogrel

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation by blocking the ADP receptor [41- 43], a mechanism independent of the thromboxane-mediated pathway inhibited by aspirin. In the CAPRIE trial, clopidogrel 75 mg/day reduced long-term risk of stroke, myocardial infarction, or vascular death by 8.7% relative to aspirin in patients with vascular disease, without increasing risk of hemorrhage or other major side effects[44]. The trial was not designed to evaluate clopidogrel as an acute therapy, and no trial has evaluated the efficacy of clopidogrel after TIA.

Clopidogrel may be useful as an acute intervention after vascular events. With a loading dose of 300 mg, clopidogrel produces platelet inhibition at steady-state levels within 2 hours[45, 46].

2.2.4 *Combination Clopidogrel-Aspirin*

Clopidogrel has been studied in combination with aspirin in several trials of vascular disease, including two that included patients with stroke or TIA. Although results from these trials have not supported long-term use of clopidogrel after stroke/TIA, the drug has never been tested as an acute therapy in this population and the trials support that it may be more beneficial and particularly safe after minor stroke or TIA.

Aspirin and clopidogrel synergistically antagonize platelet aggregation [44, 47- 49], and combined, may provide added benefit in stroke prevention. Aspirin and clopidogrel are used together after coronary, carotid, and intracranial stenting, and appear to be well tolerated [50, 51]. Evidence supporting clopidogrel also comes from cardiac trials, non-acute stroke/TIA trials, and most importantly, from an acute pilot trial of TIA and minor stroke, as reviewed below.

2.2.4.1 *Cardiac Trials*

The CURE trial of patients with acute coronary syndromes, also taking aspirin found that clopidogrel 75 mg/day after a loading dose of 300 mg reduced the risk of stroke, myocardial infarction, and vascular death by 20% at 3-12 month follow-up, and the effect was apparent in the first 10 days [52]. Myocardial infarction and vascular death accounted for the vast majority of events in this trial. There was a small increase in risk of major hemorrhage but no difference in life-threatening hemorrhage. In the CREDO study, clopidogrel also reduced the 1-year risk of cardiovascular events by 27% among those treated with aspirin undergoing percutaneous coronary intervention [53]. An early benefit was seen only in those who received a loading dose of clopidogrel 6 hours before the procedure, reinforcing the importance of an initial loading dose when ischemic events may occur within hours. There was a 1% absolute increase in risk of major bleeding at 28 days, but most of this was associated with procedures such as bypass surgery. Thus, clopidogrel reduces ischemic events in patients treated acutely after coronary ischemia or prior to percutaneous coronary intervention.

2.2.4.2 Non-Acute Stroke/TIA Trials

The MATCH (Management of atherothrombosis with clopidogrel in high-risk patients with

recent TIA or ischemic stroke) trial was a secondary stroke prevention trial that enrolled 7599 patients, mostly in Europe [54]. This study compared aspirin plus clopidogrel to clopidogrel. The majority of patients (79%) enrolled suffered a prior stroke, rather than TIA. The overall trial was negative, with a small insignificant 1% absolute benefit in terms of reduced risk of ischemic events balanced by a 1% but significant absolute increased risk of major hemorrhage. In subgroup analysis, however, there was a trend toward greater benefit in those treated sooner after the qualifying stroke or TIA, with a 17% RRR in those treated within 7 days. The CHARISMA trial randomized patients with vascular disease, who are treated with aspirin 75-162 mg/day, to clopidogrel 75 mg or placebo [55]. Similar to MATCH, the trial was negative with a small reduction in ischemic events balanced with a small significant increase in severe hemorrhages. However, also similar to MATCH, there was greater benefit in patients treated sooner after a clinical qualifying event (including stroke and TIA). In unpublished analysis of the 4320 patients enrolled in CHARISMA after TIA or stroke, a study involving Drs. Johnston and Easton (reviewed here to maintain continuity), the RRR of stroke with clopidogrel was 26% in those randomized within 30 days of the event and 17% in those randomized later, again suggesting that patients treated early are more likely to benefit. There was no increased risk of hemorrhage in those treated within 30 days or later among those randomized after stroke or TIA.

2.2.4.3 Pilot Acute TIA/Stroke Trials

FASTER [56] was a pilot trial evaluated clopidogrel (300 mg load and 75 mg/day afterwards) and simvastatin in a factorial design on a background of aspirin in patients presenting within 24 hours of a TIA or minor stroke. The main principal motivating the trial was the recognition of the high frequency of poor outcomes in patients presenting with acute cerebral ischemia who are not candidates for thrombolysis. The trial enrolled 392 patients from 18 centers over 30 months. The risk of stroke (ischemic or hemorrhagic) at 90 days was 11% in those treated with aspirin alone and 7% in those treated with clopidogrel and aspirin, a non-significant 36% RRR in this pilot trial (p=0.19). There were two intracranial hemorrhages, both in patients treated with clopidogrel-aspirin; one occurred in a patient with minor stroke and uncontrolled blood

pressure and the other occurred in a patient with TIA but details are uncertain. These hemorrhages were included in the primary outcome and did not overwhelm the benefit. The trial serves as an excellent pilot for the proposed trial, reconfirming a high risk of stroke in patients with TIA and minor stroke and suggesting that a large effect size is possible.

Another pilot double-blind, placebo-controlled trial, CARESS, evaluated the impact of clopidogrel-aspirin vs. aspirin alone on presence of TCD micro-embolic signals in 107 patients with recently symptomatic carotid stenosis [57]. At 7 days, 44% on the combination and 73% on aspirin alone had persistent micro-embolic signals (p=0.005), suggestive of a reduction in ongoing thrombo-embolism. There were more strokes and TIAs in the aspirin-only group (11 vs. 4) but the difference was not significant.

2.2.4.4 Risks of major hemorrhage

Although the trials in non-acute stroke or TIA suggest that the combination increases risk of major hemorrhage, the risk of thrombosis is extremely high in the acute period after TIA or minor stroke and risk of hemorrhage is expected to be lower than after moderate or severe stroke, so the combination may be particularly effective and relatively safe in this setting. In fact, patients with TIA or minor stroke have minimal or no infarction, so their risk of hemorrhage may be more similar to those with cardiac disease than to those with completed strokes that are disabling enough to meet entry criteria in prior trial [58]. For example, in the TOAST study, risk of serious brain bleeding with danaparoid was 14% in those with an NIH Stroke Scale score >15 and only 0.5% in those with less severe stroke [59]. Thus, hemorrhage risk with the combination of aspirin and clopidogrel should be relatively low after TIA or minor stroke.

2.3 Conclusion

TIA or minor stroke is a neglected condition. Many studies have shown that the risk of stroke is higher than completed stroke in short-term. Effective therapies in those patients could significantly reduce the overall burden of stroke if initiated immediately. Antiplatelet therapy may play a distinct role in this acute pathophysiology. However, no large-scale trial has evaluated an acute intervention in patients with TIA or minor stroke.

The FASTER pilot trial, as well as other negative trials of clopidogrel in combination with ASA after stroke or TIA suggests that treatment with the combination might be beneficial when taken soon after a TIA or minor stroke. Of course, these data are only suggestive, because they are derived from small pilot studies and subgroup analyses, and they should not be taken as proof of clinical utility, but they do provide strong supports for a large-scale clinical trial to test the aggressive antiplatelet therapy in acute minor stroke or TIA [60]. In conclusion, taking all these data into account and given the high risk of vascular events after TIA or minor stroke, especially in acute setting, it anticipated that the proposed study design can maximize the benefit while minimizing the risk of bleeding events.

3 STUDY OBJECTIVES

3.1 Primary

The primary objective of this randomized, double-blind, multicenter clinical trial is to assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 21 Days versus a 3-month regimen of aspirin 75 mg/day alone on reducing the 3-month risk of **any new stroke (ischemic orhemorrhagic)** when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.

3.2 Secondary

3.2.1. To assess the secondary composite outcome: composite of any stroke, myocardial infarction, and vascular death.

3.2.2. To assess the primary outcome measure in a Per-protocol (PP) population. This will include all patients who have not had a significant interruption of study drug (Actual number doses taken less than80% of expected number of doses taken) or major protocol violation.

3.2.3. To assess separately the effects of this Clopidogrel regimen versus ASA alone on the incidence of: new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) as a cluster and evaluated individually.

3.2.4. To evaluate change in modified Rankin Scale [mRS,(continuous)] and percentage with score 0-2 at last follow-up.

3.2.5. To compare the safety of the two treatment regimens in terms of:

- ✧ Severe or moderate bleeding (GUSTO definition, see appendix)
- ✧ Intracranial hemorrhage
- ✧ Total mortality
- ✧ AEs/SAEs
  - Thrombotic thrombocytopenic purpura (TTP)
  - Granulocytopenia
  - Hypersensitivity
  - Renal failure

3.2.6. To compare efficacy and safety by etiology, non-Intracranial artery diseases (non-ICAD) vs. ICAD (substudy)

3.2.7. To compare efficacy and safety by qualifying event, TIA vs. minor stroke.

3.2.8. To compare efficacy and safety in those previously taking ASA or Clopidogrel at presentation or not.

3.2.9. To compare efficacy and safety by gender and age (<65 years vs≥65 years).

3.2.10. In further exploratory analysis, to evaluate impairment (change in NIHSS scores), and Quality of Life (EuroQol EQ-5D scale) among survivors.

3.2.11. To compare efficacy and safety by time to randomization, < 12 hours vs. ≥ 12 hours.

3.2.12. To evaluate the primary outcome and intracranial hemorrhage in those with and without imaging evidence of infarction on the initial head CT or MRI imaging.

4 STUDY DESIGN AND MANAGEMENT OVERVIEW

4.1 Study Design Overview

The primary null hypothesis of this randomized, double-blind multicenter clinical trial is, there is no difference in 90-day risk of any new stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 21 Days versus a 3-month regimen of aspirin 75 mg/day alone when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.

Patients with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (defined as an NIHSS ≤ 3), who can be treated within 24 hours of symptom onset will be enrolled.Patientsmeeting these criteria and offering informed content will be randomized into two groups: the first group will receive a 300mg loading dose of clopidogrel on the day of randomization, followed by 75 mg clopidogrel/day from Day 2 to 3 months. Aspirin will be given in a total dose ranging between 75 mg and 300 mg (open label with dose determined by the treating physician) on the first day, followed by blinded 75 mg once /day from Day 2 to 21. Between day 21 and 3-month visits, aspirin 75 mg will be replaced by a placebo of aspirin 75 mg. The second group will receive open label aspirin in a total dose ranging between 75 mg and 300 mg on the first day, followed by 75 mg once/day from Day 2 to 3 months. A placebo for clopidogrel will be given from the day of randomization until the 3-month visit. Subjects will be followed for 90 days andrisk of any stroke (ischemic or hemorrhage) will be assessed in the treatment groups. The trial will be completed in 35 months, with 5,100 subjects recruited from about 100centers in China in partnership with research network and CHANCE Clinical Research Collaboration. A Data and Safety Monitoring Board (DSMB) will regularly monitor safety during the study.

4.2 Study Milestones

A 3-year budget and recruitment plan have been created; key study milestones below.

STUDY MILESTONES

Pre-enrollment Study Initiation	9 months (2009.01-2009.09)
Recruitment and Follow-up	19 months (2009.10- 2011.04)
Completion of Follow-up	3 months (2011.05-2011.07)
Data Analysis and Publication	4 months (2011.08-2011.11)
Total Duration	35 months

4.3 Study Organization

Principal Investigator：

Yongjun Wang, Beijing Tiantan Hospital, Beijing, China；

S. Claiborne Johnston, University of California, San Francisco, USA

The Steering committee members of CHANCE study are as follows:

Pr. Yongjun Wang (PI)

Pr. Claiborne Johnston (USA- Co PI)

Pr. L. Wong (Hong Kong)

Pr. David Wang (USA)

Pr. James Wang (USA)

Pr. Mai N. Nguyen-Huynh (USA)

Pr. Chen Wang

Pr. Liying Cui

Pr. Yansheng Li

Pr. Qiang Dong

Pr. JianfengXu

Pr. JianpingJia

Pr. Jiang Wu

Pr. JinshengZeng

Pr. Xingquan Zhao

Pr. Liping Liu

Pr. Chunxue Wang

Pr. Yilong Wang

The steering committee will provide scientific and strategic direction for the trial and will have overall responsibility for its design, execution, and publication.

The steering committee will also be responsible for ensuring that study execution and management are of the highest quality.

It will approve the protocol and the operational guidelines of the trial prior to its commencement.

The steering committee will convene regularly by teleconference or face-to-face meetings to discuss and report on the progress of the study.

The composition of the steering committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

Executive committee

The two co-chairs and additional members of the Steering Committee, including two project directors, will be members of the Executive Committee. They will convene more frequently (teleconferences or physical meetings) to review the status of the trial and available blinded data and will take appropriate actions regarding the conduct of the study.

A face-to-face Executive Committee meeting will be organized to make major decisions.

The composition of the Executive Committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

Executive committee members: Yongjun Wang, Claiborne Johnston, Yilong Wang, Xingquan Zhao, Liping Liu, Xia Meng, Anxin Wang, Jinxi Lin.

Data safety and monitoring board (DSMB)

The DSMB will meet regularly and monitor the progress of the CHANCE study to ensure that the study meets the highest standards of ethics and patient safety. It is composed of Academic Members, including an independent statistician, who are not otherwise participating in the trial. A DSMB charter including membership role and responsibilities will be approved by both the DSMB and the Executive Committee before the start of the trial.

Written recommendations and their rationale will be provided to the Chairs of the Steering Committee immediately after each DSMB meeting.

DSMB members: Hao Li, Haipeng Shen, Yilong Wang, Anxin Wang, Gaifen Liu, Xianwei Wang; Yuesong Pan.

Adjudication committee

Clinical outcome events (stroke, MI, death, overt bleedings) will be reviewed by independent experts (neurologists, cardiologists). An adjudication committee charter including membership, role and responsibilities will be approved before the start of the trial by the Adjudication Committee and the Executive Committee.

Neuroimaging associated with clinical events will be read locally and reports will be included in adjudication packets. The adjudication committee may request actual images from sites or from the core lab in special instances.

Members of adjudication committee: Lawrence. Wong (Hong Kong), David Wang (USA), James Wang (USA), Yansheng Li, Anding Xu, Peiyi Gao.

4.4 Site Training, Certification, and Update

Executive committee have already provided training to their sites in Good Clinical Practice Guidelines and in some outcome assessments (e.g., NIHSS, mRS).

Prior to initiation of patient enrollment, Site Investigators and Coordinators will complete training programs and their certifications. In these training modules, the patient selection criteria and follow-up procedures will be reviewed. Case studies illustrating potential problems in adhering to study protocol and blinding will be discussed.

All investigators must complete the following training modules, and receive certification:

- Study procedures
- Primer on the diagnosis of TIA and its mimics
- Use of the $ABCD^2$ score
- CHANCE eligibility
- Modified Rankin Scale
- NIHSS
- SSS-TOAST
- EQ-5D
- Outcome events adjudication
- GUSTO
- Collecting blood sample only for subgroup
- Collecting DICOM imaging data only for subgroup

Successful completion of the training program will be required before a site is certified to enroll patients. Telephone-based meetings, with the PI and key staff available to address questions, will occur intermittently. Certification of competence will be obtainable on the four training centers.

A detailed Manual of Procedures will serve as the primary document describing all study related procedures. It will serve as a guide for training of clinical center personnel and will be updated periodically throughout the study on the CHANCE website, as needed. A system composed of members of executive committee and clinical research associate will be implemented for the clinical centers to call, fax, or e-mail any procedural questions regarding the study. The CHANCE executive committee will formulate answers in consultation with the Steering Committee, and will periodically distribute to the participating centers a set of frequently asked questions (FAQ) and answers. These questions and answers will be available on the study website.

The members of executive committee will manage and conduct site visits for its sites and ensure the integrity and validity of the data recorded on the Case Report Forms. Each site will be visited at least once during the trial, and as needed if questions about data quality or problems with recruitment arise.

4.5 Contact Schedule and Measurements

Subject encounters will include screening, randomization,21st day visit,and 90th day visitora final event visit. In addition, event visits are to occur whenever patient contact suggests that a patient experiences a potential clinical neurological event, including a clinical deterioration that could be possibly related to ischemia, or new transient or persistent neurological symptoms, an adjudication packet will be produced by the site within 72 hours.

4.6 Outcomes

The definitions of endpoint outcomes are given in Appendix 1.

4.6.1 Primary Efficacy Endpoint

Percentage of patients with the 3-month new vascular events, defined as any event of the following:

- *Any stroke (ischemic or hemorrhagic)*

4.6.2 Secondary Efficacy Endpoint

- Percentage of composite of any stroke, myocardial infarction, and vascular death within 3 month.
- Patients with the 3-month new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) evaluated individually.
- Modified Rankin Scale score changes (continuous) and dichotomized at percentage with score 0-2 vs. 3-6 at 3 month follow-up (Scale is described in Appendix 2).
- Further efficacy exploratory analysis:
  - ✧ Impairment (changes in NIHSS scores at 3 month follow-up), (Scale is described in Appendix 3).
  - ✧ Quality of Life (EuroQol EQ-5D scale, described in Appendix 4).
- Efficacy endpoint will also be analyzed stratified by etiological subtypes (non-ICAD vs. ICAD), by time randomization (< 12 hours vs. ≥ 12 hours), by qualifying event (TIA vs. minor stroke), and by age (<65 years vs≥65 years).

4.6.3Safety Endpoint

4.6.3 .1 Clinical Safety

Clinical safety will be assessed by:

- ✧ A physical examination including neurological evaluation at D1, 21th day and M3 visits.
- ✧ Adverse event collection at each visit after baseline
- ✧ Measurement of supine blood pressure and heart rate at each visit.

4.6.3 .2 Adverse Event Collection

No specific laboratory safety tests are required during this study. However, if a laboratory abnormality is clinically relevant or leads to an adverse event report, specific appropriate actions may be required (see Appendix 5, decision charts).

4.6.3 .3 Electrocardiogram

An ECG will be performed at the baseline visit (Day 1).

4.6.3 .4 Safety Endpoint

4.6.3.4.1 Primary safety endpoints

- ✧ Incidence of severe bleedingor moderate bleeding (GUSTO definition, see appendix 6), including fatal bleeding and symptomatic intracranial hemorrhage

4.6.3.4.1 Secondary safety endpoints

- ✧ Incidence of symptomatic and asymptomatic intracranial hemorrhagic events at 3 months
- ✧ Total mortality
- ✧ AEs/SAEs reported by the investigators

5 PARTICIPANT SELECTION

During the course of the trial, about 100sites will enroll 5,100 subjects with TIA or minor ischemic stroke. Before enrolling patients into the study, all collaborating sites will obtain approval from local Institutional Review Boards (IRBs), which will have access to all study documentation and educational materials.

5.2 Study Population

Inclusion Criteria

- Adult subjects (male or female ≥ 40 years)
- Acute non-disabling ischemic stroke (NIHSS≤3 at the time of randomization) that can be treated with study drug within 24 hours of symptoms onset. Symptom onset is defined by the "last see normal" principle.
- TIA (Neurological deficit attributed to focal brain ischemia, with resolution of the

deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate-to-high risk of stroke recurrence (ABCD2 score ≥ 4 at the time of randomization). Symptom onset is defined by the "last see normal" principle.

- Informed consent signed

Exclusion Criteria

- Diagnosis of hemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major non-ischemic brain disease (e.g., multiple sclerosis) on baseline head CT or MRI.
- Isolated or pure sensory symptoms (e.g., numbness), isolated visual changes, or isolated dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI.
- Modified Rankin Scale Score > 2 at randomization (pre-morbid historical assessment)
- NIH Stroke Score ≥ 4 at randomization
- Clear indication for anticoagulation (presumed cardiac source of embolus, e.g., atrial fibrillation, prosthetic cardiac valves known or suspected endocarditis).
- Contraindication to clopidogrel or ASA.
    - Known allergy
    - Severe renal or hepatic insufficiency
    - Severe cardiac failure, asthma
    - Hemostatic disorder or systemic bleeding
    - History of hemostatic disorder or systemic bleeding
    - History of thrombocytopenia or neutropenia
    - History of drug-induced hematologic or hepatic abnormalities
    - Low white blood cell (<2 x109/l) or platelet count (<100 x109/l).

- Use of thrombolysis within 24 hours prior to randomization

- History of intracranial hemorrhage.
- Anticipated requirement for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function.
- Current treatment (last dose given within 10 days before randomization) with heparin therapy or oral anti coagulation.
- Gastrointestinal bleed or major surgery within 3 months.
- Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months (if clinically indicated, vascular imaging should be performed prior to randomization whenever possible)
- Scheduled for surgery or interventional treatment requiring study drug cessation.
- Qualifying TIA or minor stroke induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy < 3 months.
- Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- Currently receiving an investigational drug or device.

6 TREATMENTS

6.1 Study Drugs

This randomized double-blind study is primarily designed to compare a clopidogrel/aspirin combination versus an aspirin alone regimen. The two types of study tablets (75 mg active clopidogrel and placebo) are indistinguishable, identical in size, shape, color, appearance, and taste.

Minor side effects are unusual with the medication, so it is not anticipated that either subjects or clinicians will be able to differentiate the placebo from the active drug. Standard laboratory

tests cannot detect the effects of clopidogrel.

Investigators will not have access to the randomization (treatment) code, except in exceptional circumstances, such as occurrence of a serious adverse event for which knowledge of the study medication would be considered essential for treating the subject.

6.2 Formulations

- ✧ Clopidogrel 75 mg tablets
- ✧ Placebo tablets of Clopidogrel 75 mg
- ✧ ASA 75 mg tablets
- ✧ Placebo tablets of ASA 75 mg

6.3 Route of administration

- ✧ Oral

6.4 Dose regimen

Group 1:

- ✧ Day 1*: four tablets of clopidogrel 75 mg and open label ASA (75 mg -300 mg)
- ✧ From D2 to D21±2 days: one tablets of clopidogrel 75mg and one tablet of ASA 75 mg per day
- ✧ From D22±2 days visit to D90±7 days(does not exceed 75 days between D21±2 days visit to D90±7 days): one tablets of clopidogrel 75mg and one tablet of placebo ASA 75 mg per day

*On Day1, patients will receive open label ASA (between 75-300 mg) with dose at the discretion of the investigator. This represents the total dose given on D1(between75-300 mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day.

Group 2:

- ✧ Day 1*: four tablets of placebo clopidogrel 75 mg and open label ASA (75 mg -300 mg)

- From D2 to D21±2 days: one tablets of placebo clopidogrel 75mg and one tablet of ASA 75 mg per day
- From D22±2 days visit to D90±7 days(does not exceed 75 days between D22±2 days visit to D90±7 days): one tablets placebo of clopidogrel 75mg and one tablet of ASA 75 mg per day.

*On Day1, patients will receive open label ASA (between 75-300 mg) with dose at the discretion of the investigator. This represents the total dose given on D1 (between 75-300 mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day.

Study drug will be started **as soon as possible** after randomization (within one hour).

7 STUDY DRUG HANDLING

7.1 Supply and Storage

Sanofi-Aventis will supply the blinded investigational products (study drug and placebo) used in the study. All investigational drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individual, and under the conditions described on the labeling.

7.2 Packaging and Labeling

Each patient will be assigned a "patient kit" according to the randomization list.

According to the study periods and visits, each patient kit will consist of both the public box and the patient box that includes two boxes. Each box is composed of two parts as following:

Public box including the open-label aspirin (A_0)

Two wallets of the packaging for 1st day: the first one is 50mg* 12 pills *15 pieces; the other one is 25mg * 30 pills * 1 piece. ASA in public box is available to 30 patients.

Patient box including box 1 and box 2

Box 1 composed of two wallets: the first one is non-open-label clopidogrel or placebo clopidogrel (C1) containing 75mg * 7 pills * 4 pieces for period from Day 1 to Day 21 ± 2. The other one is non-open-label ASA (A1) containing 25mg * 30 pills * 2 piece + 6 pills for period from Day 2 to Day 21 ± 2.

Box 2 composed of two wallets for period from Day 21± 2 to Day 90± 7: the first one is non-open-label clopidogrel or placebo clopidogrel (C2) containing 75mg * 7 pills * 11 pieces. The other one is non-open-label ASA or placebo ASA (A2) containing 25mg * 30 pills * 8 pieces.

The content of the labeling will be in accordance with the local regulatory specifications and requirements.

7.3 Responsibilities

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product will be responsible for ensuring that the Investigational Product used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All Investigational Product shall be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pel1aining documentation, labeling, expiry date, etc.) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply Investigational Product to a third party, allows the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

7.4 Concurrent Treatment

7.4.1 Prohibited Concomitant Treatments

Use of the following medications after randomization and during the study period represents a protocol violation. However, if there is a clinical need that justifies the added risk of these interventions in the setting of study drug use, they should be employed at the discretion of the treating physician

- ✧ Open-label ASA (with the exception of day 1, see Figure 1)
- ✧ NSAIDs, Cox1 and Cox2 inhibitors. If absolutely necessary, NSAIDs may be given for less than 5 days but not sooner than 8 days after randomization
- ✧ Open-label thienopyridines (ticlopidine, clopidogrel)
- ✧ Dipyridamole
- ✧ All heparins
- ✧ Oral anticoagulants
- ✧ GPIIbIIIa receptor antagonists
- ✧ Thrombolytics
- ✧ Vascular intervention (surgery and / or angioplasty of any vessel). If intervention is absolutely necessary within the three months period after randomization, study drug will be stopped 5 days prior to the intervention. Study treatment will then be restarted unless the patient needs to take open label clopidogrel or aspirin. In this case, study drug will be restarted only when treatment with open label antiplatelet therapy has been stopped.

7.4.2 Permitted Concurrent Treatments

Any drugs other than those listed above are permitted (including anti-hypertensive medications), if considered necessary for the patient, with a stable dose (when possible), at the discretion of the Investigator. Given uncertainty about an interaction between omeprazole and

other proton pump inhibitors and clopidogrel, those previously taking a proton-pump inhibitor will be evaluated for the appropriateness of other agents, such as H_2 blockers. New prescriptions for proton-pump inhibitors will be avoided whenever an H_2 blocker or other agent is an acceptable option. Similarly, other drugs that theoretically may affect clopidogrel metabolism will be avoided, with others substituted. This list includes: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), and fluvoxamine (Luvox).

Any treatment which is ongoing before randomization and/or prescribed or changed during the study must be recorded in the CRF.

7.4.3 Treatment Accountability and Compliance

Compliance will be assessed by counting returned tablets at each visit.

The investigator (or delegates) will complete the appropriate page of the CRF or study drug inventory log form.

The date of study drug interruption must also be recorded.

7.5 Treatment Discontinuation

The investigational product (IP) should be continued whenever possible. If the IP is stopped, it should be determined if the discontinuation can be made temporarily; permanent IP discontinuation should be a last resort. Any IP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

7.5.1 Temporary treatment discontinuation with investigational product(s)

Re-initiation of treatment with the Investigational Product will be done under close and appropriate clinical/and or laboratory monitoring (see Appendix 5 Decision Charts) once the Investigator has considered according to his/her best medical judgment that the role of the

Investigational Product(s) in the occurrence of the event concerned was unlikely and there is no other contraindication to continuing in the study.

All temporary treatment discontinuation (< 10 days) and the date of treatment re-initiation should be recorded by the Investigator on the appropriate CRF pages when considered to be confirmed

7.5.2 Definition treatment discontinuation with investigational product(s)

A patient should discontinue the study drug for any of the following reasons:

- ✓ Intercurrent condition that requires discontinuation of the study (e.g. lab abnormalities, Appendix 5).
- ✓ Positive serum pregnancy test or desire to become pregnant
- ✓ Contraception cessation

7.5.3 Handling of patients after definitive treatment discontinuation

Patients will be followed according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of an AE, whichever comes last

All withdrawals should be recorded by the Investigator on the appropriate CRF pages when considered to be confirmed

All patients who have discontinued the study drug prior to the last visit should have a complete end-of-study visit at three months.

For patients considered lost to follow-up, the CRF must be completed up to the last visit performed. The Investigator should make every effort to contact the patient and to identify the reason why he/she failed to attend the visit and to determine his/her health status

7.5.4 Consequence

Patients who have been withdrawn from the study cannot be included again in the study. Their patient number and treatment must not be re-used.

The investigator will call the IVRS to notify the treatment discontinuation and/or the patient's withdrawal.

Randomized patients will not be replaced.

7.5.5 Retrieval and/or destruction of treatments

A detailed log of returned Investigational Product will be established by the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the partially used or unused Investigational Product unless the Sponsor provides written authorization to the contrary.

A potential defect in the quality of Investigational Product may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

7.6 Blinding System and Emergency Unblinding Procedure

7.6.1 Description of blinding methods

This randomized double-blind study is primarily designed to compare a clopidogrel /ASA combination followed by clopidogrel alone regimen versus an ASA alone regimen.

The two types of clopidogrel tablets developed (75 mg active clopidogrel and placebo clopidogrel) are indistinguishable (identical in size, shape, color, appearance).

The two types of ASA tablets developed (75 mg active ASA and placebo ASA) are indistinguishable (identical in size, shape, color, appearance).

No locally- used biological test that could potentially unblind the treatment is planned in this study.

Investigators will not have access to the randomization (treatment) code, except in exceptional circumstances, such as occurrence of a serious adverse event for which knowledge of the study medication would be considered essential for treating the subject.

7.6.2 Method of assigning patients to a treatment group

The randomization code list will be generated centrally by a Contract Research Organization (CRO).

The patient kits will be packaged in accordance with this randomization code list. During the treatment period, the patient will receive study medication corresponding to either the clopidogrel / ASA group or the ASA group using a randomization ratio of 1:1.

Randomization will be stratified according to the time from symptoms onset to randomization (＜12 hours or ≥12 hours).

The treatment number will be allocated using a centralized treatment allocation system (Inter-voiceResponse System, IVRS) on D1 (baseline visit). Before randomizing a patient, the investigator will have to contact the IVRS and give some information (such as study number, patient date of birth and initials, study site, and time between symptom onset and randomization). A treatment number will then be given to the investigator, who will give the first box of the corresponding package to the patient.

7.6.3 Access to the randomization code during the study

In case of an Adverse Event, the code may be broken only in exceptional circumstances when knowledge of the Investigational Product is essential for treating the patient. If possible, contact should be made with the Monitoring Team before breaking the code.

If the physician at the investigational site believes unblinding is needed, he/she must call the IVRS 24-hour unblinding service. All the calls will be documented by the CRO.

If the blind is broken, the Investigator will document the date, time of day and reason for the code break. Study drug will not be resumed afterwards.

8 SAFETY

8.1 Adverse Events Monitoring

All events will be managed and reported in compliance with all applicable regulations and will be included in the final Clinical Study Report (CSR).

8.2 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Efficacy endpoints will not be considered as AEs except if, because of the course or severity or any other features of such events, the Investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- ✓ Results in death, or
- ✓ Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- ✓ Requires inpatient hospitalization or prolongation of existing hospitalization, or
- ✓ Results in persistent or significant disability/incapacity, or
- ✓ Is a congenital anomaly/birth defect, or
- ✓ Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

These should also usually be considered serious.

Note: Examples of such events 3re intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions or asymptomatic ALT increase ≥ 10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

8.3 Obligation of the investigator regarding safety reporting

8.3.1 Adverse Events

All Adverse Events regardless of seriousness or relationship to Investigational Product, spanning the time from the first visit planned in the Clinical Trial Protocol/signature of the informed consent (i.e., occurring during the washout period) to the last visit planned in the protocol, are to be recorded on the corresponding page(s) included in the Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the Investigational Product.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

8.3.2 Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately:

SEND (within 1 working day, preferably by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and fax number appear on the Clinical Trial Protocol;

ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly noted on any copy of source documents provided to the Sponsor. For laboratory results, include the laboratory normal ranges;

Follow-up of any Serious Adverse Event that is fatal or life threatening should be provided within one additional calendar week.

8.3.3 Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients; notably, he should follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or stabilization of the patient's condition;

In the case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;

In the case of any Serious Adverse Event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered.

10 STUDY PROCEDURES

9.1 Day 1 visit = Screening, inclusion or baseline visit

9.1.1 Screening and Inclusion

Inclusion and exclusion criteria will be assessed, and:

$ABCD^2$ score for TIA patients and neurological evaluation (Modified Rankin Scale and NIHSS) will be performed for screening subjects

An electrocardiogram (ECG) will be performed (12-lead) to rule out atrial fibrillation. A head CT or MRI scan will be required to rule out hemorrhage, vascular malformation, tumor, or abscess. Since ECG and head imaging are recommended for all patients presenting with TIA and minor stroke, the study will not cover these costs.

A screening form will be completed for all patients in whom enrollment is considered. These screening forms will be useful in determining whether specific groups of patients are under-represented in the study and to confirm participation of sites.

The patient will receive complete information about the study, both orally and in writing.

Those meeting all inclusion criteria and no exclusion criteria (see Section 5) will be invited to participate. Consent will be obtained directly from the subject prior to enrollment. .

9.1.2 Baseline Evaluation

Baseline evaluation will include patient demographic information, symptoms of the index event, medications, past medical history, family history, cigarette and alcohol use, examination findings, pretreatment Rankin Score.

Laboratory tests will be performed (serum creatinine, glycemia, neutrophil count (or at least a total WBC count) and platelet count)

A physical examination will be performed, including measurement of weight (kg) and vital signs (supine systolic and diastolic blood pressure, heart rate)

Results of head imaging, CBC, and ECG will be recorded using standardized instruments. .

9.1.3 Randomization

The statistician will develop a master randomization list, with stratification blocked to assure an equal distribution of treatments at each participating site. If the subject was confirmed, the investigator will call the IVRS for randomization and treatment group allocation. This system will allow Clinical Sites to perform participant enrollment around the clock, 7 days a week. A study number will correspond to a specific medication packet. This identifying number will be coded on the enrollment confirmation.

9.1.4 Treatment on DAY 1

The patient will receive Day 1 study medication and be instructed how to take the study medication. Time of first study drug administration will be recorded.

Study drug will be started as soon as possible after randomization (within 24 hours after onset).

ASA will be given at the discretion of the investigator, at a total dose for Day 1 between 75 and

300 mg.

The following information will be collected for each patient:

- ✓ Demographic (age, sex, ethnic origin)
- ✓ Patient's medical history and concomitant diseases
- ✓ Concomitant medications
- ✓ An appointment will be made for next study visit (D21 ± 2 days after randomization)

9.2 Day 21 Visit = D 21±2

During this visit:

- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)
- ✓ A physical examination will be performed, including vital signs (supine systolic and diastolic blood pressure, heart rate)
- ✓ Information will be collected on concomitant medications and adverse events since the last visit
- ✓ Treatment Box 1 with unused study medication from completed study period (with Day 1 and Day 2 to Day 21±2 wallets) will be collected for drug accountability and assessment of treatment compliance
- ✓ Treatment Box 2 (from Day 21±2 visit to Day 90±7 visit and does not exceed 75 days from D21±2 to D90±7) will be dispensed to the patient and he will be instructed how to take the study drug until next visit
- ✓ An appointment will be made for next study visit (three months ± 7 days after randomization)

9.3 Three month Visit = D 90±7

Note: Number of days between D21±2 and D 90±7 visits may not exceed 75 days.

During this visit:

- ✓ If the patient will be diagnosed by sICAD, MRI+MRA (MRI including T1 + T2 + DWI + FlAIR + T2*) sequences will be strongly encouraged to perform. Images will be transferred to the core imaging evaluation lab.
- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)
- ✓ Quality of life scale (EQ-5D) will be performed in a quiet room (Appendix 4)
- ✓ A physical examination will be performed, including vital signs (supine systolic and diastolic blood pressure, heart rate)
- ✓ Information will be collected on concomitant medications and adverse events since the last visit
- ✓ The treatment box from completed study period with unused study medication will be collected for drug accountability and assessment of treatment compliance

9.4 Possible event visit

If a patient experiences a potential clinical neurological event, including a clinical deterioration that could be possibly related to ischemia, or new transient or persistent neurological symptoms, an adjudication packet will be produced by the site within 72 hours. This will include the following:

- ✓ A neurological evaluation will be performed (Modified Rankin Scale and NIHSS)
- ✓ A physical examination will be performed, including measurement of weight (kg) and vital signs (supine systolic and diastolic blood pressure, heart rate)
- ✓ **If the patient will be diagnosed by sICAD, MRI (including T1 + T2 + DWI + FlAIR + T2*) sequences will be strongly encouraged to perform. Images will be transferred to the core imaging evaluation lab.**
- ✓ If a patient experiences a new potential cardiac event, a cardiac evaluation (including ECG) will be performed as clinically indicated. Information supporting a possible myocardial infarction will be collected in an adjudication packet and transmitted to the CRO within 72 hours.

- ✓ Information will be collected on concomitant medications and adverse events since the last visit.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis Plans

This section is an overview of the statistical considerations. Complete details can be found in the Statistical Analysis Plan (SAP). It provides the general specifications for the analysis of the data to be collected and presented in the Clinical Study Report. A final SAP will be issued prior to database lock and before code breaking. The SAP will define all "pre-specified, planned analyses."

10.1.1 Sample Size Estimates

10.1.1.1 Primary Null Hypothesis

In patients with TIA or minor ischemic stroke treated with aspirin 75 mg/day, there is no difference in 90-day risk of stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day compared to placebo when therapy is initiated within 24 hours of symptom onset.

The minimum necessary sample size in the trial is established by the requirement to detect the smallest expected, clinically meaningful treatment difference comparing the treatment with placebo. A relative risk reduction of 22% (relative risk [RR] with addition of clopidogrel is 0.78) is the smallest difference we will attempt to detect.

With a sample size of 5100 patients, we will have 90% power to detect a relative risk reduction of 22% with a two-sided alpha of 0.05, and 5% drop outs (medication non-adherence) (Table 2 and Figure 2). The sample size formula used was based on the usual comparisons of proportions in two groups. This formula should provide more conservative estimates given that we plan a survival analysis for the trial.

Table 2. Sample size calculations for various risks (12% to 17%) of outcome in control (ASA) group

Power	n without drop outs	n with 5% drop outs	Risk of outcome in treatment group	Risk of outcome in control group	Relative risk with addition of clopidogrel
0.8	2880	3024	13%	17%	0.78
0.8	3094	3249	12%	16%	0.78
0.8	3334	3501	12%	15%	0.78
0.8	**3608**	**3788**	**11%**	**14%**	**0.78**
0.8	3926	4122	10%	13%	0.78
0.8	4296	4511	9%	12%	0.78
0.9	3856	4049	13%	17%	0.78
0.9	4140	4347	12%	16%	0.78
0.9	4462	4685	12%	15%	0.78
0.9	**4830**	**5072**	**11%**	**14%**	**0.78**
0.9	5254	5517	10%	13%	0.78
0.9	5750	6038	9%	12%	0.78

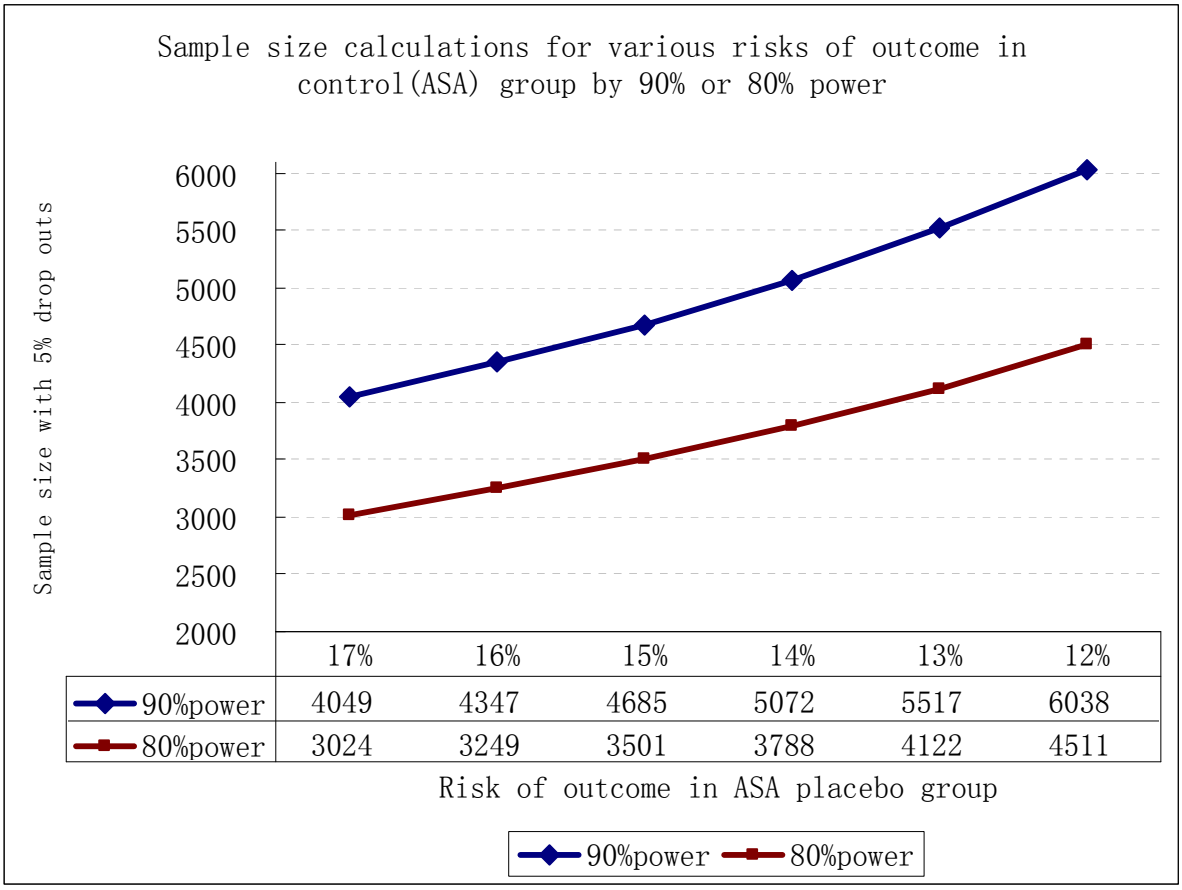


Figure 2. Sample size calculations for various risks of outcome in control (ASA) group by 90% or 80% power

10.1.1.1.1Risk of outcome in placebo (ASA) group

Based on the pooled Northern California and Oxfordshire cohort study[62] and FASTER trial[56], the 90-day risk of the stroke recurrence risk in this group is about 14% among high-risk TIA (ABCD2 score > 4) or minor stroke patients treated with ASA within 24 hours of symptom onset.

Table 3. Risk estimation of outcome in placebo (ASA) group

Population	n	3-month Risks	
		Stroke	Stroke / MI / Death
All TIA[1]	2776	10.30%	12.14%

Excluding low-likelihood[1]	2325	11.87%	14.02%
ABCD[2] score in TIA[1]			
> 3	2067	12.58%	14.42%
> 4	1379	14.72%	16.75%
> 5	737	17.50%	19.94%
TIA and minor stroke [2]	194	10.8%	11.9%

[1] Based on the pooled Northern California and Oxfordshire cohort study[62].

[2] FASTER trial[56].

10.1.1.1.2 Relative risk with addition of clopidogrel to ASA

We anticipate that clopidogrel will reduce risk of the composite outcome—stroke, myocardial infarction, and vascular death—independent of ASA. The relative risk reduction (RRR) of clopidogrel compared to placebo demonstrated in the FASTER pilot trial was 34.3% (for any stroke), but confidence intervals were broad given its small size. Other estimates of RRR can be obtained from subgroup analyses of trials with broader entry criteria, though these include subgroups (esp, stroke) that we don't anticipate will respond as well, and treat patients for long periods of time, when the risk of drug remains and benefit is likely lower. In the CHARISMA trial, patients with stroke/TIA treated with clopidogrel-ASA within 21 days of stroke or TIA had a 24% RRR compared to ASA alone. In the MATCH trial, a RRR of 17% was demonstrated in patients treated within 7 days of stroke or TIA for ASA-clopidogrel compared to clopidogrel alone. Given prior safety results, we do not anticipate excess intracerebral or life-threatening hemorrhage with clopidogrel in patients with TIA. Therefore, inclusion of intracerebral hemorrhage in the composite outcome is not expected to reduce the apparent benefit of clopidogrel. Based on these prior studies, we suspect the RRR will be greater than 22% (Figure 3).

Figure 3. Impact of clopidogrel-ASA vs. either alone based on timing of enrollment after clinical event (Outcome: stroke, MI, or vascular death)

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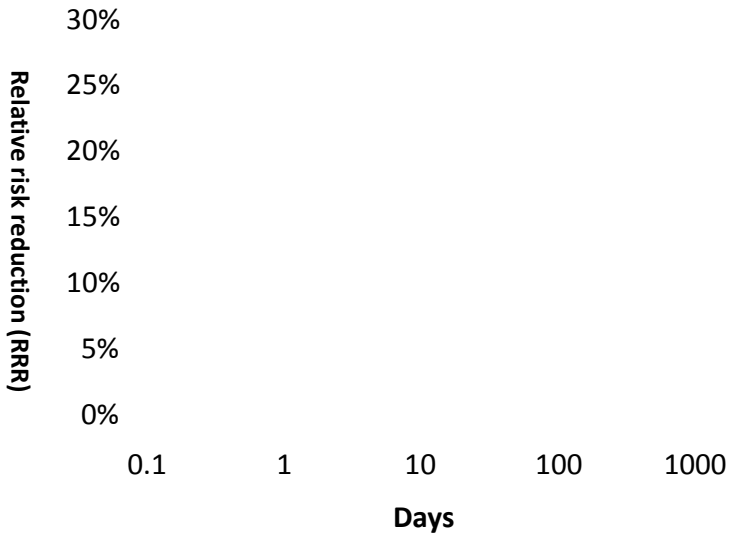

10.1.1.1.3 Clinical significance of relative risk

Sample size is based on the desire to detect a 22% relative risk reduction. With this relative risk reduction, treatment of 32 patients with TIA or minor stroke (regardless of other risk factors) would be expected to result in one fewer stroke event over 3 months, based on the pilot study results. This effect is likely to be considered clinically important by treating physicians; this level of benefit is greater than that of ASA in secondary prevention after stroke, and ASA is widely accepted and utilized in this setting.

10.1.1.1.4 Delay between symptom onset and enrollment

Strokes may occur before randomization due to delays in enrollment. Patients with events occurring within 24 hours of TIA symptom onset were eliminated from the analysis of event rates since many of these patients would not have been enrolled and treated before the outcome occurred.

10.1.1.1.5 Losses to follow-up/non-adherence

These computations allow for a 5% rate of drop outs (medication non-adherence).

10.1.1.1.6 Power and alpha

Given the uncertainty in the assumptions used to predict effect size and event rates, we have chosen a sample size to provide 90% power (two-sided test, at the 5% difference level).

In summary, approximately 2550 patients per arm (5100 total) will give 90% power to detect a relative risk reduction of 22% with a two-sided alpha of 0.05, and 5% drop outs (medication non-adherence) (Table 2, Figure 2) 22% (relative risk [RR] with addition of clopidogrel is 0.78).

10.2 Statistical Analyses

A detailed statistical analysis plan will be created during the start-up period of the trial, which will include all tables and details of all analyses.

10.2.1 Primary Outcomes

The primary analysis will be intention to treat, with inclusion determined by receipt of first study drug dose. Missing values will remain missing and patients will be censored at their last follow-up assessment (time of clinical event, end of study, or last visit prior to loss to follow-up). Time to randomization was presented with group mean. Differences between treatments in the risk of stroke (ischemic or hemorrhagic) event during maximum 90-day follow-up were assessed using standard Kaplan-Meier time-to-event approaches, and the hazards ratios with 95% CI were reported. The time to the first event was used in the model when there were multiple events of the same type. This approach is being taken to maximize the time dependent information in the trial while still acknowledging the ease of interpretation of risks. All statistics will be two-sided with $p<0.05$ considered significant.

10.2.2 Secondary Outcomes

The analysis strategy outlined for the primary outcome will be used for most of the secondary analyses. For continuous outcomes (such as NIHSS and mRS), we will use a multiple linear regression analysis. Continuous outcomes will be checked for approximate normality and heteroscedasticity of residuals and for outliers. Transformations and/or weighted least squares will be considered as remedies for non-normality and heteroscedasticity. Outliers will be checked for validity and their influence on conclusions will be tested in sensitivity analyses.

11 ETHICAL AND REGULATORY STANDARDS

11.1 Ethical principles

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice.

11.2 Laws and regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, and Chinese laws and regulations in which the Clinical Trial is performed, as well as any applicable guidelines.

11.3 Informed consent

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

11.4 Institutional Review Board/Independent Ethics Committee(IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC)

composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form,

Investigator's Brochure, Investigator's CV, etc.), the list of voting members along with their qualification and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Clinical Trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

If requested, a progress report will be sent to the Ethics Committee (IRB/IEC) annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

12 STUDY MONOTORING

12.1 Responsibilities of the investigator(s)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical

Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. During these monitoring visits, the following, but not exhaustive, points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

12.2 Source document requirements

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre- identified

source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRS/IEC), and the regulatory authorities to have direct access to source data which support the data on the Case Report Forms (e.g., patient's medical file, appointment books, original laboratory records, etc.). Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

12.3 Use and completion of Case Report Forms(CRFS) and additional requests

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to the Sponsor's instructions) all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated.

The CRFs will be faxed (data fax system) visit per visit or collected at each routine monitoring visit.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests (ORF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the CRFs held by the Investigator and the Sponsor.

12.4 Use of computerized systems

Computerized systems will be used to create, modify, maintain, archive, retrieve and transmit data (IVRS, monitoring tool, data entry and statistical analysis).

13 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. The trial results will be published as soon as possible after database lockdown.

This trial will produce detailed data on treatment effects, medical care, and outcomes in a cohort of 5100 subjects with TIA or minor ischemic stroke. CHANCE biostatisticians will be consulted to assure that it is impossible to uniquely identify any participant. This may mean removing or categorizing certain variables. A data use agreement will not be required for access to this dataset. Diskettes with the data in comma-delimited text format will be sent to parties that express interest, including a data dictionary in a text file.

14 ANCILLARY STUDIES

Proposals for ancillary studies will be reviewed by the Executive Committee. Sites will not be required to participate in any ancillary study that requires additional data collection, but they will be encouraged to participate in accepted studies. Publication of the results of these studies will be governed by the policies and procedures developed by the Executive Committee.

15 REFERENCES

1. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH,Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. Lancet Neurol 2007;6(5):456-64.

2. Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. Circulation 2001;103(3):462-8.

3. Shi FL, Hart RG, Sherman DG,Tegeler CH. Stroke in the People's Republic of China. Stroke 1989;20(11):1581-5.

4. Brown RD Jr, Petty GW, O'Fallon WM, WiebersDO,Whisnant JP.Incidence of transient ischemic attack in Rochester, Minnesota, 1985-1989. Stroke 1998;29(10):2109-13.

5. Wolf, P.A. and L.A. Cupples. Incidence and prevalence of transient ischemic attack. In: W.S. Moore, ed. Surgery for Cerebrovascular Disease. New York:Churchill Livingstone,1987.

6. Edlow JA, Kim S, Pelletier AJ,Camargo CA Jr. National study on emergency department visits for transient ischemic attack, 1992-2001. AcadEmerg Med 2006;13(6):666-72.

7. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998;29(2):415-21.

8. Yi Long Wang, Di Wu, Xiaoling Liao, Wei Zhang, Xingquan Zhao, Yong Jun Wang.Burden of stroke in China. International Journal of Stroke 2007;2(3):211-213.

9. Wang W, Zhao D, Wu G, Liu J, Liu S, Qin L, et al. Trend analyses in the incidence of acute intracerebral hemorrhage events and acute cerebral infarction events in urban areas in Beijing. Zhonghua Liu Xing Bing XueZaZhi 2002;23(5):352-5.

10. Jiang B, Wang WZ, Chen H, Hong Z, Yang QD, Wu SP, et al. Incidence and trends of stroke and its subtypes in China: results from three large cities. Stroke 2006;37(1):63-8.

11. Zhao D, Liu J, Wang W, Zeng Z, Cheng J, Liu J, et al. Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project. Stroke

2008;39(6):1668-74.

12. Rothwell PM, Buchan A,Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. Lancet Neurol 2006;5(4):323-31.

13. Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Jimenez-Conde J, Pont-Sunyer C, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke 2008;39(6):1717-21.

14. Johnston SC, Gress DR, Browner WS,Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284(22):2901-6.

15. Coull AJ, Lovett JK,Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328(7435):326.

16. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36(4):720-3.

17. Gladstone DJ, Kapral MK, Fang J, LaupacisA,Tu JV. Management and outcomes of transient ischemic attacks in Ontario. CMAJ 2004;170(7):1099-104.

18. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, SvensonLW,Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62(11):2015-20.

19. Eliasziw M, Kennedy J, Hill MD, Buchan AM,Barnett HJ. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ 2004;170(7):1105-9.

20. Friedman GD, Wilson WS, Mosier JM, ColandreaMA,Nichaman MZ. Transient ischemic attacks in a community. JAMA 1969;210(8):1428-34.

21. Ueda K, Kiyohara Y, Hasuo Y, Yanai T, Kawano H, Wada J, et al. Transient cerebral ischemic attacks in a Japanese community, Hisayama, Japan. Stroke 1987;18(5):844-8.

22. Whisnant JP, Matsumoto N,Elveback LR. Transient cerebral ischemic attacks in a community. Rochester, Minnesota, 1955 through 1969. Mayo ClinProc 1973;48(3):194-8.

23. Dennis MS, Bamford JM, SandercockPA,Warlow CP. A comparison of risk factors and prognosis for transient ischemic attacks and minor ischemic strokes.TheOxfordshire Community Stroke Project. Stroke 1989;20(11):1494-9.

24. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333(24):1581-7.

25. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. Neurology 2005;64(4):654-9.

26. Weinberger J. Antiplatelet agents for stroke prevention following transient ischemic attack. South Med J 2008;101(1):70-8.

27. Emre U, RantanenK,Tatlisumak T. Antithrombotic treatment in the prevention of ischemic stroke. Curr Drug Targets 2007;8(7):817-23.

28. Albers GW. Antithrombotic therapy for prevention and treatment of ischemic stroke. J Thromb Thrombolysis 2001;12(1):19-22.

29. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349(9066):1641-9.

30. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349(9065):1569-81.

31. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31(6):1240-9.

32. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38(5):1655-711.

33. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA, et al. National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol 2006;60(3):301-13.

34. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39(5):1647-52.

35. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37(2):577-617.

36. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25(5):457-507.

37. Halkes PH, van Gijn J, Kappelle LJ, KoudstaalPJ,Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006;367(9523):1665-73.

38. Diener HC, Cunha L, Forbes C, Sivenius J, SmetsP,Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J NeurolSci 1996;143(1-2):1-13.

39. Diener HC, Sacco R,Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). Cerebrovasc Dis 2007;23(5-6):368-80.

40. Ralph L. Sacco, on behalf of the PRoFESS Study Group. Prevention Regimen For Effectively avoiding Second Strokes - The PRoFESS Trial Results. Presented at European Stroke Conference 2008.

41. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. Drugs 2007;67(4):613-46.

42. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. Drugs 2000;60(2):347-77.

43. Sharis PJ, Cannon CP,Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. Ann Intern Med 1998;129(5):394-405.

44. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348(9038):1329-39.

45. Helft G, Osende JI, Worthley SG, Zaman AG, Rodriguez OJ, Lev EI, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. ArteriosclerThrombVascBiol 2000;20(10):2316-21.

46. Savcic M, Hauert J, Bachmann F, Wyld PJ, GeudelinB,Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. SeminThrombHemost 1999;25Suppl 2:15-9.

47. Herbert JM, Dol F, Bernat A, Falotico R, LaleA,Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. ThrombHaemost 1998;80(3):512-8.

48. Harker LA, Marzec UM, Kelly AB, Chronos NR, Sundell IB, Hanson SR, et al. Clopidogrel

inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. Circulation 1998;98(22):2461-9.

49. Makkar RR, Eigler NL, Kaul S, Frimerman A, Nakamura M, Shah PK, et al. Effects of clopidogrel, aspirin and combined therapy in a porcine ex vivo model of high-shear induced stent thrombosis. Eur Heart J 1998;19(10):1538-46.

50. Jauhar R, Bergman G, Savino S, Deutsch E, Shaknovich A, Parikh M, et al. Effectiveness of aspirin and clopidogrel combination therapy in coronary stenting. Am J Cardiol 1999;84(6):726-8, A8.

51. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99(18):2364-6.

52. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, TognoniG,Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(7):494-502.

53. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288(19):2411-20.

54. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364(9431):331-7.

55. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354(16):1706-17.

56. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, DemchukAM,Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised

controlled pilot trial. Lancet Neurol 2007;6(11):961-9.

57. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111(17):2233-40.

58. Hart RG, Easton JD. Do we really need a better way to give heparin in acute cerebral ischemia?. Stroke 2002;33(3):659-60.

59. Adams HP Jr, Woolson RF, Clarke WR, Davis PH, Bendixen BH, Love BB, et al. Design of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Control Clin Trials 1997;18(4):358-77.

60. Johnston SC. Towards FASTER treatment of TIA and minor stroke. Lancet Neurol 2007;6(11):941-3.

61. Salthouse TA. The role of memory in the age decline in digit-symbol substitution performance. J Gerontol 1978;33(2):232-8.

62. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369(9558):283-92.

16 APPENDIXS

Appendix 1: Definition of End Points

Stroke	Sudden symptoms and signs of focal disturbance of cerebral function associated with cerebral circulation disorders. Etiology would be classified based on SSS-TOAST standard.
Ischemic stroke	An acute focal infarction of the brain or retina. Criteria: (1) acute onset of a new focal neurological deficit with clinical or imaging evidence of infarction lasting more than

	24 hours and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or (2) acute onset of a new focal neurological deficit and not attributable to a non-ischemic etiology lasting less than 24 hours, but accompanied by neuroimaging evidence of new brain infarction; or, (3) rapid worsening of an existing focal neurological deficit lasting more than 24 hours and not attributable to a non-ischemic etiology, and accompanied by new ischemic changes on brain MRI or CT, and clearly distinct from the index ischemic event.
Hemorrhagic stroke	An acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurological symptoms.
TIA	A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain. Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)
Symptomatic intracerebral hemorrhage	Any extravascular blood in the brain associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Intracerebral hemorrhage is defined as an acute extravasation of blood into the brain parenchyma. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy

Asymptomatic intracerebral hemorrhage	an acute extravasation of blood into the brain parenchyma without clinical deterioration. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy
Other symptomatic intracranial hemorrhage	Any extravascular blood within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Other Asymptomatic intracranial hemorrhage	An acute extravasation of blood into the subarachnoid space, epidural space, or subdural space without associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Myocardial infarction with coronary revascularization	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, treated with coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Myocardial infarction without coronary	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, not treated with

revascularization	coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Coronary Revascularization without myocardial infarction	A procedure to improve coronary blood flow for documented coronary artery disease, but with no documentation of myocardial infarction. Criteria: Documented coronary angioplasty, stenting, or bypass surgery for demonstrated or presumed coronary artery disease
Ischemic vascular death	Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause
Hemorrhagic Vascular death	Death due to intracranial or systemic hemorrhage

Appendix 2: modified Rankin Scale

The modified Rankin Scale (mRS) is a scale commonly used for measuring the degree of disability or dependence in the daily activities of individuals who have suffered a stroke, and it has become the most widely used clinical outcome measure for stroke clinical trials.

Description	**Score** (select one)
No symptoms at all	**0** ☐
No significant disability despite symptoms; able to carry out all usual duties	**1** ☐

and activities	
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	**2** ☐
Moderate disability; requiring some help, but able to walk without assistance	**3** ☐
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	**4** ☐
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	**5** ☐

Appendix 3: NIH Stroke Scale

Administer stroke scale items in the order listed. Record the performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	**Scale Definition**	**Score**
1a. Level of Consciousness: The investigator must choose a response 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, and flexic.	_____

Instructions	Scale Definition	Score
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 him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
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;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is 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. Patients may 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 respond to item 11.	**0 = No visual loss.** **1 = Partial hemianopia.** **2 = Complete hemianopia.** **3 = Bilateral hemianopia** (blind including cortical blindness).	_____

Instructions	Scale Definition	Score
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. 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 barriers obscure the face, these should be removed to the extent possible.	**0 = Normal**symmetrical movements. **1 = Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). **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. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 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, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	**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.** **UN** = Amputation or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____

Instructions	Scale Definition	Score
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls 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 leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	**0 = No drift;** leg holds 30-degree 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.** **UN** = Amputation or 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 of visual defect, ensure 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, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	**0 = Absent.** **1 = Present in one limb.** **2 = Present in two limbs.** **UN = Amputation or joint fusion**, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick 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 sensory loss," 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 brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically 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 of being touched. **2 = Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____

Instructions	Scale Definition	Score
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, 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 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 a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for 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.	**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 materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. **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 barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	**0 = Normal.** **1 = Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood with some difficulty. **2 = Severe dysarthria;** 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. **UN = Intubated** or other physical barrier, explain:_____ ___	_____

Instructions	Scale Definition	Score
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 extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____
	Total NIHSS:	_____

Appendix 4: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

☐I have no problems in walking about

☐I have no problems in walking about

☐I am confined to bed

Self-Care

☐I have no problem with self-care

☐I have some problems washing or dressing myself

☐I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure activities)

☐I have no problems with performing my usual activities

☐I have some problems with performing my usual activities

☐I am unable to perform my usual activities

Pain/discomfort

☐I have no pain or discomfort

☐I have moderate pain or discomfort

☐I have extreme pain or discomfort

Anxiety/depression

☐I am not anxious or depressed

☐I am moderately anxious or depressed

☐I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

how good or bad
your own health is today

Questionnaire completed by:

☐$_1$Patients independently

☐$_2$Patients with help of others

☐ $_3$Agent (the patient's family members)

Appendix 5: Abnormal clinical laboratory indicators

bleeding tendency	Prothrombin time >1.5 times control or platelet count<10×10^9/L
moderate or severe anemia	Hemoglobin (Hb)<90g/L
abnormal liver function	Transaminase beyond the normal more than two times
Abnormal renal function	Serum creatinine>1.5mg/dl or creatinine clearance rate<50ml/min

Appendix 6: GUSTO classification

Severe Bleeding	Documented intracranial hemorrhage or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention (other than vascular site repair), or CPR to maintain a sufficient cardiac output.
Moderate Bleeding	Bleeding that requires transfusion of blood but does not lead to hemodynamic compromise requiring intervention.
Mild Bleeding	Bleeding not requiring' transfusion and not causing hemodynamic compromise. This includes subcutaneous bleeding, mild hematomas, oozing from puncture sites, etc.

Summary of protocol amendments

APPENDIX Ⅰ:

Protocol changes version 1.0 (Jan 03, 2009) to 1.1 (Feb. 25, 2009)

✧ Dose regimen (page 33): For Group 1, duration of combination of aspirin 75 mg/day is changed from first 30 (±7) days into first 21(±2) days.

✧ Study procedures (page 43): hospital discharge is deleted and Day 30 Visit is changed into Day 21 Visit.

APPENDIX Ⅱ:

Protocol changes version 1.1 (Feb. 25, 2009) to 1.2 (Mar. 15, 2009)

✧ 10.1.1 Sample Size Estimates (10.1.1.1 Primary Null Hypothesis, page 47; 10.1.1.1.6 Power and alpha, page 52): 80% statistical power to detect a relative risk reduction of 22% is changed into 90% power. Therefore, sample size of 3800 will be replaced by 5100.

APPENDIX Ⅲ:

Protocol changes version 1.2 (Mar. 15, 2009) to 1.3 (May 20, 2009)

✧ Study objectives (3.2 Secondary, page 22): two subgroups are added.

3.2.11. To compare efficacy and safety by time to randomization, < 12 hours vs. ≥ 12 hours.

3.2.12. To evaluate the primary outcome and intracranial hemorrhage in those with and without imaging evidence of infarction on the initial head CT or MRI imaging.

✧ Number of Centers: Up to about 80 investigational sites in the China in Clinical Research Network is change into about 100 sites.

✧ 7.4.2 Permitted Concurrent Treatments (page 37): proton-pump inhibitors are avoided with consideration for between omeprazole and other proton pump inhibitors and clopidogrel. So, the following content is added:

Given uncertainty about an interaction between omeprazole and other proton pump inhibitors and clopidogrel, those previously taking a proton-pump inhibitor will be evaluated for the appropriateness of other agents, such as H2 blockers. New prescriptions for proton-pump inhibitors will be avoided whenever an H2 blocker or other agent is an acceptable option. Similarly, other drugs that theoretically may affect clopidogrel metabolism will be avoided, with others substituted. This list includes: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), and fluvoxamine (Luvox).

APPENDIX Ⅳ:

Protocol changes version 1.3 (May 20, 2009) to 1.4 (July 25, 2009)

✧ 4.3 Study Organization (page 25):

- Pr. Chen Wang is added to Steering committee members
- Names of executive members are added: Yongjun Wang, Claiborne Johnston, Yilong Wang, Xingquan Zhao, Liping Liu, Xia Meng, Anxin Wang, Jinxi Lin.
- DSMB members changed: **from** Hao Li, Yilong Wang, Yong Zhou **into** Hao Li, Haipeng Shen, Yilong Wang, Anxin Wang, Gaifen Liu, Xianwei Wang; Yuesong Pan.
- Members of adjudication committee added as follows: Lawrence. Wong (Hong Kong), David Wang (USA), James Wang (USA).

Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE)

Statistical Analysis Plan

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Version 1.0

Jan 20, 2009

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Introduction

This statistical analysis plan (SAP) documents the planned statistical analyses for the CHANCE study and is based on the protocol, together with any subsequent amendments.
This SAP is intended for the use of project team members within Beijing Tiantan Hospital, and should be read in conjunction with the aforementioned protocol.

Study Objective(s) and Endpoint(s)

Study Objective(s)

The primary objective of this study is to assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 30 Days versus a 3-month regimen of aspirin 75 mg/day alone on reducing the 3-month risk of any new stroke (ischemic or hemorrhagic) when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.

The secondary objectives of this study are:

- To assess the secondary composite outcome: composite of any stroke, myocardial infarction, and vascular death
- To assess separately the effects of this Clopidogrel regimen versus ASA alone on the incidence of: new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) as a cluster and evaluated individually.
- To assess whether there are differential treatment effects in predefined subgroups:
  - (<65 years vs ≥65 years)
  - Sex (male vs female)
  - Index event (minor stroke vs TIA)
  - TIA risk stratification ($ABCD^2$=4 vs $ABCD^2$>4)
  - Previous stroke
  - Previous TIA
  - History of hypertension
  - History of diabetes
  - Systolic blood pressure at baseline (<140mmHg vs ≥140mmHg)
  - Aspirin taken within 24h
- To assess the primary outcome measure in a Per-protocol (PP) population. This will include all patients who have not had a significant interruption of study drug (Actual number doses taken less than 80% of expected number of doses taken) or major protocol violation.

Other objectives are:

- To evaluate treatment differences if changes in modified Rankin Scale[1] from baseline to the last follow-up.
- To compare the safety of the two treatment regimens in terms of:
  - Severe or moderate bleeding (GUSTO definition)[2]
  - Intracranial hemorrhage
  - Total mortality
  - AEs/SAEs

- In further exploratory analysis, to evaluate treatment differences of impairment (change in NIHSS scores)[3], and Quality of Life (EuroQol EQ-5D scale)[4] among survivors.

Study Endpoint(s)

Primary Efficacy

- Rate of new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period.

Secondary Efficacy

- Rate of the composite outcome: including any stroke, myocardial infarction, and vascular death as a cluster and evaluated individually

Other Efficacy

- Changes of the Modified Rankin Scale scores between the end of study and baseline.
- Further efficacy exploratory analysis:
  - ✧ Changes in NIHSS scores between the end of study and baseline.
  - ✧ Changes in EuroQol EQ-5D scale between the end of study and baseline.

Safety Endpoint

- Rate of moderate and severe bleeding incidence (GUSTO definition), including fatal bleeding and symptomatic intracranial hemorrhage
- Rate of symptomatic and asymptomatic intracranial hemorrhagic events at 3 months
- Rate of total mortality
- Incidence of AEs/SAEs (as described in the protocol) reported by the investigators

Clinical safety will be assessed by a physical examination including neurological evaluation at at D1, hospital discharge, Ml and M3 visits. Adverse events will be collected at each visit after baseline. Supine blood pressure and heart rate will be measured at each visit. No specific laboratory safety tests are required during this study. However, if a laboratory abnormality is clinically relevant or leads to an adverse event report, specific appropriate actions may be required (see Appendix 5, decision charts). An ECG will be performed at the baseline visit (Day 1).

Statistical Hypotheses

The primary endpoint for this study will be the rate of new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period.
The null hypothesis of no difference in this rate between the two treatment groups will be tested using a two-sided test at the 5% level of significance
H_0: $\lambda_1/\lambda_2 = 1$
H_1: $\lambda_1/\lambda_2 \neq 1$
Where λ_1 is the rate of new stroke over the 3-month treatment period in the group treated with Clopidogrel/ASA regimen and λ_2 is the same endpoint in the group treated with ASA alone.

Study Design

The primary null hypothesis of this randomized, double-blind multicenter clinical trial is, there is no

difference in 90-day risk of any new stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 30 Days versus a 3-month regimen of aspirin 75 mg/day alone when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke..

Patients with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (defined as an NIHSS ≤ 3), who can be treated within 24 hours of symptom onset will be enrolled. Patients meeting these criteria and offering informed content will be randomized into two groups: the first group will receive a 300mg loading dose of clopidogrel on the day of randomization, followed by 75 mg clopidogrel/day from Day 2 to 3 months. Aspirin will be given in a total dose ranging between 75 mg and 300 mg (open label with dose determined by the treating physician) on the first day, followed by blinded 75 mg once /day from Day 2 to 30. Between day 31 and 3-month visits, aspirin 75 mg will be replaced by a placebo of aspirin 75 mg. The second group will receive open label aspirin in a total dose ranging between 75 mg and 300 mg on the first day, followed by 75 mg once/day from Day 2 to 3 months. A placebo for clopidogrel will be given from the day of randomization until the 3-month visit. Subjects will be followed for 90 days and risk of any stroke (ischemic or hemorrhage) will be assessed in the treatment groups. The trial will be completed in 35 months, with 3,800 subjects recruited from about 80 centers in China in partnership with research network and CHANCE Clinical Research Collaboration. A Data and Safety Monitoring Board (DSMB) will regularly monitor safety during the study.

Planned Analyses

The analyses that are detailed in this SAP will be performed only when the database has been frozen, all protocol violators identified and treatment allocations have been unblinded. The treatment allocations will be unblinded and extracted from the RandAll system. These will then be merged on to the study database using the treatment number (as allocated to each subject by RAMOS) to match subjects with the correct treatment allocation. Membership of the Intent-to-Treat and Per Protocol populations will be determined using the rules set out in this SAP and will be determined prior to unblinding the treatment allocation. At a date to be agreed within the project team, a data look will be performed. This will involve production of all data displays on a subset of the data using dummy treatment codes. These are produced purely as an aide to the pre-programming of the study and no unblinding will occur.

Interim Analyses

No interim analyses are planned for this study. However, a Data and Safety Monitoring Board (DSMB) is in place to ensure the safety of subjects in the study. An independent statistician will prepare unblinded summary tables of SAEs, selected demographic data and subject exposure data and these will be examined by the DSMB. These tables will be provided to the DSMB at regular intervals. If the tables give rise to safety concerns for any treatment, the DSMB may recommend that the trial should be modified or stopped prematurely. The Steering Committee will, in conjunction with the Sponsor, decide whether to act on this recommendation. Further discussion of these safety tabulations is provided in a specific study protocol.

Sample Size Considerations

Sample size for the study assumed that the number of new stroke events (ischemic or hemorrhagic) would follow a Poisson distribution. The rate of new stroke events was expected to be 0.14 per subject within 3-month after Day 1 in the ASA alone treated group based on a previous study[5]. It was expected that the Clopidogrel/ASA treated group would reduce this by 22%; this is equivalent to 0.11 exacerbations per subject within 3-month after Day 1. With this relative risk reduction, treatment of 32 patients with TIA or minor stroke (regardless of other risk factors) would be expected to rescue one stroke event over 3 months. With a sample size of 3800 patients, we will have 80% power to detect a relative risk reduction of 22% with a two-sided alpha of 0.05, and 5% drop outs (medication non-adherence).

Analysis populations

Total Population

This population will comprise of all subjects screened and for whom a record exists on the study database. This population will be used for listing adverse events occurring prior to randomization and reasons for withdrawal occurring prior to randomization.

Intent-to-Treat Population

The Intent-to-treat (ITT) population will comprise of all subjects Randomized to treatment and who received at least one dose of trial medication. Randomized subjects will be assumed to have received trial medication unless definitive evidence to the contrary exists.
The ITT Population will be used for tables of efficacy, demography, safety, health outcomes, listings of withdrawals after randomization, and all relevant listings. This population will be the primary population for analyses of efficacy and safety.

Per Protocol population

The Per Protocol (PP) population will consist of all subjects in the ITT population not identified as protocol violators. The decision to exclude a subject from the PP population will be made prior to breaking the blind. This population will be used for secondary analyses of the primary efficacy measure. The decision to exclude a subject from the Per Protocol Population will be made prior to breaking the study blind. A partial protocol violator will be included in the Per Protocol Population up to the time of their violation. For the Per Protocol Population, subjects will be analyzed according to the treatment received, providing the same treatment was taken for the duration of the study. If study medication was changed then the subject will be considered a partial protocol violator (from the point of change onwards).

Treatment comparisons

The treatment comparison of interest in this study is between clopidogrel /ASA combination followed by clopidogrel alone regimen and an ASA alone regimen over the 90-day treatment period, based on the ITT population.

General considerations for data analyses

All programming will be performed using SAS Version 9.0. All analysis output will use the following treatment group naming conventions and treatment order:
clopidogrel /ASA for a loading dose of clopidogrel 300mg followed by clopidogrel 75 mg /day day 2-90 plus blinded aspirin 75 mg once /day day 2-30 and then aspirin placebo day 31-90
ASA for clopidogrel placebo on day 1, followed by aspirin 75 mg/day plus clopidogrel placebo day 2-90
Unless otherwise specified all significance tests will be 2-sided at the alpha=0.05 level and all confidence intervals will be 95%.

Multicenter Studies

As stated in the protocol, centers with less than 20 subjects will be pooled with larger centers within the same geographic region; this ensures centers are of a reasonable size for the purpose of the statistical analyses. This process will be performed and finalized before the treatment codes are unblinded.

Examination of Subgroups

The rate of new stroke (ischemic or hemorrhagic) and clinical vascular event (ischemic stroke, hemorrhagic stroke, MI, vascular death) at 90 days will be presented for each level of the covariates listed previously. The extent to which the treatment effect varies across levels of each subgroup will be assessed through interaction tests.

Multiple Comparisons and Multiplicity

A single primary efficacy variable has been defined for this study, with all other efficacy variables identified as secondary or other. Similarly only one treatment comparison is of interest in the study and therefore there are no requirements to adjust for multiple comparisons or multiple endpoints within this study.

Data handling conventions

Premature Withdrawal and Missing Data

If any subject withdraws prematurely from the study (prior to the final visit D90±7 days assessment), they are required to complete the withdrawal visit in the CRF. The reasons for withdrawal will be presented in a summary table. For the purposes of summaries and analysis of clinic visit data, this visit will be assigned to the next scheduled clinic visit for that subject, regardless of whether the date falls within the next visit window.

Subjects who withdraw before the end of the study, but who do provide at least one post-baseline measure for a particular endpoint, will be included in the analysis.
Subjects who do not attend any visits after randomization will be excluded from analysis of new stroke and clinical vascular event rates, and safety outcomes, as no post-baseline data will be available.

Event Rates

Summary tables will calculate endpoint event rates (e.g. new stroke, safety outcomes) per 3-month in the following way. The number of 4-week periods that the subject was on treatment for will be rounded up to the next integer. The number of events that a subject had will be divided by the number of 4-week periods, and then multiplied by 3, to give an event rate per 3-month e.g.;

- Number of 4-week periods = round up (number of weeks on treatment / 4)
- Number of event rate per 3-month = 3 × number of events / no of 4-week periods.

For example if a subject had 2 events then withdrew after 3 weeks of treatment

- Number of 4-week periods = round up (3/4) = round up (0.75) = 1
- Number of event rate per 3-mo=3 × (number of events / no of 4-week periods) = 3 × (2 / 1) = 6.

Using 1-month periods in this way means that it is not likely that a subject will have unreasonably high value, which could happen if it was assumed the rate per time was constant. In the example above assuming a constant rate would have lead to a value of 9 events per 3-month, whereas using this method leads to a value of 6 per year.
The average event rate for each treatment group will be calculated as: the sum of number of event for all the patients / the sum of number of 4-week treatment periods for all the patients.

Time to Event Analysis

Differences between treatments in the risk of new stroke (ischemic or hemorrhagic) event and combined vascular events during maximum 90-day follow-up were assessed using standard Kaplan-Meier time-to-event approaches. The time to the first event was used in the model when there were multiple events of the same type. Patients were considered censored at the time of study termination or death if there were no events occurred during the study.

Study Population

Disposition of Subjects

The number of subjects in each analysis population will be presented, subjects to be excluded from the Per Protocol population will be listed, and the total number of subjects attending each clinic visit will also be summarized by treatment group.
The number of subjects Randomized, completed and prematurely withdrawn from the study will be presented for each treatment group. The primary reasons for withdrawal both prior to and post randomization will also be presented.
A data display listing and summary of deviations from the inclusion/exclusion criteria will be presented for all subjects who were either entered or Randomized into the trial.

Protocol Deviations

Subject data will be examined for evidence of protocol violators in order to assess how well the protocol was followed. Inclusion and exclusion criteria are detailed in the study protocol.
Subjects who commit protocol violations will be included in the ITT Population but excluded from the Per Protocol Population. These protocol violations will be shown in a listing. Subjects can either be full or partial protocol violators. A full protocol violator is completely excluded from the Per Protocol Population. A partial protocol violator has only some data excluded. For subjects who violated the protocol during the treatment period due to unpermitted changes in the medication or prohibited concurrent medication, the analysis will only use data recorded prior to the violation.
For all violations which reference the treatment period, the treatment start date will be used as the reference date.
A listing of all possible protocol violators will be produced for clinical review. The final list of subjects who are protocol violators and are therefore excluded from the Per-Protocol population will be agreed by the study team prior to unblinding the study.

Demographic and Baseline Characteristics

The following demographic information will be listed and summarized for subjects in each treatment group: age, sex, body mass index (BMI). This will also be done for smoking history, stroke and TIA history, symptoms of the index event, past medical history, family history, alcohol use, pretreatment Rankin Score and NIHSS score.
Laboratory tests will be listed and summarized for subjects in each treatment group including serum creatinine, glycemia, neutrophil count, and platelet count.
Vital signs including supine systolic blood pressure, diastolic blood pressure, and heart rate will also be listed and summarized in each treatment group.
Qualifying TIA baseline $ABCD^2$ score will be summarized by treatment group.

Treatment Compliance

The overall percentage compliance will be calculated separately for the doses taken for clopidogrel/ASA and ASA alone group using the following formula:

$$\frac{\text{Actual number doses taken}}{\text{Expected number of doses to be taken}} * 100$$

Where expected number of doses taken = [treatment stop date - treatment start date+1].
This data will be listed and summarized for all subjects by treatment group, in addition the number and percent of subjects falling into the following categories will be presented: <20%, 20-<50%, 50-<80% and ≥80%.

Efficacy Analyses

All hypothesis tests for main effects will use a 2-sided test at the 5% level of significance.

Primary Efficacy Analysis

The primary endpoint is the rate of new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period.

Main Model

The time to first new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period for the ITT Population will be summarized by treatment group using Kaplan-Meier estimates[6]. The hazard ratio for the treatment comparison will be derived using a Cox's proportional hazards model, including the pooled study center as a random effect. The hazards ratios with 95% CI will be reported.
This will also be presented graphically on a Kaplan-Meier plot.

Interactions with Subgroups

Summary tables will be produced for the predefined subgroups and interactions between treatment and these subgroups will be investigated, using a Cox proportional hazard model, with pooled study center as a random effect. A separate model will be used for each interaction to determine its significance.
This will also be presented graphically on a tree plot.

Secondary Efficacy Analyses

Rate of combined vascular events during the 3-month treatment period

The rate of combined vascular events occurring during the treatment will be analyzed using a Cox proportional hazard model similar to that in the previous section, with the pooled study center as a random effect. A combined vascular event was defined as any of the 4 following events: ischemic stroke, hemorrhagic stroke, myocardial infarction, or death from cardiovascular causes. This will also be presented graphically on a Kaplan-Meier plot.
Each of the 4 vascular events will also be analyzed using the same method and the event rate for each event will be calculated for each treatment group.

Death from any causes

The rate of overall death for any cause will be analyzed using a Cox proportional hazard model similar to that in the previous section, with the pooled study center as a random effect. The death rate will be calculated for each treatment group.

Other Efficacy Analyses

Disability measure

Changes of the modified Rankin Scale (mRS) between the end of study and baseline will be summarized for the two treatment groups among the survivors during the study. The treatment difference will be tested using student t-test.

Neurological impairment

Changes of NIHSS scores between the end of study and baseline will be summarized for the two treatment groups among the survivors during the study. The treatment difference will be tested using student t-test.

Quality of life

Health related quality of life will be measured using EuroQol EQ-5D scale among the survivors. Treatment differences will be tested using student t-test.

Time to withdrawal

The time to withdrawal data will be summarized by treatment group, and compared between treatment groups using Kaplan-Meier estimates.
The hazard ratio for the treatment comparison will be derived using a Cox's proportional hazards model, using time to withdrawal as the outcome variable.
This will also be presented graphically on a Kaplan-Meier plot.
In addition, there is potential for differential effects during the early phase of treatment, and thus treatments will also be compared using the Wilcoxon test.

Safety Analyses

All analyses of safety data will be carried out using the ITT population.

Extent of Exposure

The extent of exposure will be calculated as the number of days between start of treatment and end of treatment (i.e. treatment stop date – treatment start date + 1), and categorized into months: <1, 1-2, 2-3 months. Exposure will then be summarized by treatment group.

Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary (Version 6.0 or a later release) and grouped by system organ class (as detailed in the study protocol). Separate data display listings and summaries will be presented for adverse events that start prior to first dose of study medication (pre-treatment), whilst on study medication (during treatment) and after the last dose of study medication (post-treatment).
Within each treatment group, the number and percentage of subjects experiencing an AE will be summarized by system organ class and preferred term and Fisher's Exact test will be used to compare the number of each grouped AE event between treatment groups. In addition, a separate summary will be provided for AEs experienced by more than 5% of subjects in either of the treatment groups.

Deaths and Serious Adverse Events

Summary tables and data displays will be provided for serious adverse events (as detailed in the study protocol). In addition, all deaths and serious AE's will be documented in a case narrative format in the clinical study report.
The number of deaths occurring over the treatment period will be summarized and Fisher's Exact test will

be used to compare the number of deaths between treatment groups.

Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Summary tables will be provided of adverse events leading to discontinuation of study drug and/or withdrawal of the subject.

Pregnancies (as applicable)

Any pregnancies reported during this study will be summarized in case narratives.

REFERENCES

1. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med 1957;J 2(5):200–15.
2. Investigators. TG. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine 1993;329(10):673-82.
3. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.
4. Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. Annals of Medicine 2001;33(5):337-43.
5. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. The Lancet 2007;369(9558):283-92.
6. Andersen P, Gill, RD. Cox's regression model for counting processes: a large sample study. . Annals of Statistics 1982;10:1100-20.

Attachments

Appendix 1: Definition of End Points

Stroke	Sudden symptoms and signs of focal disturbance of cerebral function associated with cerebral circulation disorders. Etiology would be classified based on SSS-TOAST standard.
Ischemic stroke	An acute focal infarction of the brain or retina. Criteria: (1) rapid onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or, (2) rapid worsening of an existing focal neurological deficit that either (a) persists and is not attributable to a non-ischemic etiology (not associated with brain edema, infection, trauma, tumor, seizure, metabolic disease, or degenerative neurological disease) OR (b) is accompanied by evidence of new acute ischemic changes in the brain seen on an imaging study and clearly differentiated from those due to the index ischemic event.
TIA	A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain. Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)
Symptomatic intracerebral hemorrhage	Any extravascular blood in the brain associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Intracerebral hemorrhage is defined as an acute extravasation of blood into the brain parenchyma. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy
Asymptomatic intracerebral hemorrhage	an acute extravasation of blood into the brain parenchyma without clinical deterioration. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy
Other symptomatic intracranial hemorrhage	Any extravascular blood within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy

Other Asymptomatic intracranial hemorrhage	An acute extravasation of blood into the subarachnoid space, epidural space, or subdural space without associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Myocardial infarction with coronary revascularization	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, treated with coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Myocardial infarction without coronary revascularization	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, not treated with coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Coronary Revascularization without myocardial infarction	A procedure to improve coronary blood flow for documented coronary artery disease, but with no documentation of myocardial infarction. Criteria: Documented coronary angioplasty, stenting, or bypass surgery for demonstrated or presumed coronary artery disease
Ischemic vascular death	Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause
Hemorrhagic Vascular death	Death due to intracranial or systemic hemorrhage

Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE)

Statistical Analysis Plan

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Introduction

This statistical analysis plan (SAP) documents the planned statistical analyses for the CHANCE study and is based on the protocol, together with any subsequent amendments.
This SAP is intended for the use of project team members within Beijing Tiantan Hospital, and should be read in conjunction with the aforementioned protocol.

Study Objective(s) and Endpoint(s)

Study Objective(s)

The primary objective of this study is to assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with aspirin 75 mg/day during the first 21 Days versus a 3-month regimen of aspirin 75 mg/day alone on reducing the 3-month risk of any stroke (both ischemic and hemorrhagic) when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor ischemic stroke.

The secondary objectives of this study are:

- To assess the secondary composite outcome: composite of any stroke, myocardial infarction, and vascular death
- To assess separately the effects of this Clopidogrel regimen versus ASA alone on the incidence of: new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) as a cluster and evaluated individually.
- To assess whether there are differential treatment effects in predefined subgroups:
  - (<65 years vs ≥65 years)
  - Sex (male vs female)
  - Index event (minor stroke vs TIA)
  - TIA risk stratification ($ABCD^2$=4 vs $ABCD^2$>4)
  - Previous stroke
  - Previous TIA
  - History of hypertension
  - History of diabetes
  - Systolic blood pressure at baseline (<140mmHg vs ≥140mmHg)
  - Time to randomization (<12 hours vs ≥12 hours)
  - Aspirin taken within 24h
- To assess the primary outcome measure in a Per-protocol (PP) population. This will include all patients who have not had a significant interruption of study drug (less than a total of 10 days off study drug) or major protocol violation.

Other objectives are:

- To evaluate treatment differences if changes in modified Rankin Scale[1] from baseline to the last follow-up.
- To compare the safety of the two treatment regimens in terms of:
  - Severe or moderate bleeding (GUSTO definition)[2]
  - Intracranial hemorrhage
  - Total mortality
  - AEs/SAEs

- In further exploratory analysis, to evaluate treatment differences of impairment (change in NIHSS scores)[3], and Quality of Life (EuroQol EQ-5D scale)[4] among survivors.

Study Endpoint(s)

Primary Efficacy

- Rate of new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period.

Secondary Efficacy

- Rate of the composite outcome: including any stroke, myocardial infarction, and vascular death as a cluster and evaluated individually

Other Efficacy

- Changes of the Modified Rankin Scale scores between the end of study and baseline.
- Further efficacy exploratory analysis:
  - ✧ Changes in NIHSS scores between the end of study and baseline.
  - ✧ Changes in EuroQol EQ-5D scale between the end of study and baseline.

Safety Endpoint

- Rate of moderate and severe bleeding incidence (GUSTO definition), including fatal bleeding and symptomatic intracranial hemorrhage
- Rate of symptomatic and asymptomatic intracranial hemorrhagic events at 3 months
- Rate of total mortality
- Incidence of AEs/SAEs (as described in the protocol) reported by the investigators

Clinical safety will be assessed by a physical examination including neurological evaluation at Day 1, D21 and D90 visits. Adverse events will be collected at each visit after baseline. Supine blood pressure and heart rate will be measured at each visit. No specific laboratory safety tests are required during this study. However, if a laboratory abnormality is clinically relevant or leads to an adverse event report, specific appropriate actions may be required (see Appendix 5, decision charts). An ECG will be performed at the baseline visit (Day 1).

Statistical Hypotheses

The primary endpoint for this study will be the rate of new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period.
The null hypothesis of no difference in this rate between the two treatment groups will be tested using a two-sided test at the 5% level of significance
H_0: $\lambda_1/\lambda_2 = 1$
H_1: $\lambda_1/\lambda_2 \neq 1$
Where λ_1 is the rate of new stroke over the 3-month treatment period in the group treated with Clopidogrel/ASA regimen and λ_2 is the same endpoint in the group treated with ASA alone.

Study Design

The primary null hypothesis of this randomized, double-blind multicenter clinical trial is, there is no difference in 90-day risk of any new stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day combined with

aspirin 75 mg/day during the first 21 Days versus a 3-month regimen of aspirin 75 mg/day alone when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke..

Patients with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (defined as an NIHSS ≤ 3), who can be treated within 24 hours of symptom onset will be enrolled. Patients meeting these criteria and offering informed content will be randomized into two groups: the first group will receive a 300mg loading dose of clopidogrel on the day of randomization, followed by 75 mg clopidogrel/day from Day 2 to 3 months. Aspirin will be given in a total dose ranging between 75 mg and 300 mg (open label with dose determined by the treating physician) on the first day, followed by blinded 75 mg once /day from Day 2 to 21. Between day 22 and 3-month visits, aspirin 75 mg will be replaced by a placebo of aspirin 75 mg. The second group will receive open label aspirin in a total dose ranging between 75 mg and 300 mg on the first day, followed by 75 mg once/day from Day 2 to 3 months. A placebo for clopidogrel will be given from the day of randomization until the 3-month visit. Subjects will be followed for 90 days and risk of any stroke (ischemic or hemorrhage) will be assessed in the treatment groups. The trial will be completed in 35 months, with 5,100 subjects recruited from about 100 centers in China in partnership with research network and CHANCE Clinical Research Collaboration. A Data and Safety Monitoring Board (DSMB) will regularly monitor safety during the study.

Planned Analyses

The analyses that are detailed in this SAP will be performed only when the database has been frozen, all protocol violators identified and treatment allocations have been unblinded. The treatment allocations will be unblinded and extracted from the RandAll system. These will then be merged on to the study database using the treatment number (as allocated to each subject by RAMOS) to match subjects with the correct treatment allocation. Membership of the Intent-to-Treat and Per Protocol populations will be determined using the rules set out in this SAP and will be determined prior to unblinding the treatment allocation. At a date to be agreed within the project team, a data look will be performed. This will involve production of all data displays on a subset of the data using dummy treatment codes. These are produced purely as an aide to the pre-programming of the study and no unblinding will occur.

Interim Analyses

No interim analyses are planned for this study. However, a Data and Safety Monitoring Board (DSMB) is in place to ensure the safety of subjects in the study. An independent statistician will prepare unblinded summary tables of SAEs, selected demographic data and subject exposure data and these will be examined by the DSMB. These tables will be provided to the DSMB at regular intervals. If the tables give rise to safety concerns for any treatment, the DSMB may recommend that the trial should be modified or stopped prematurely. The Steering Committee will, in conjunction with the Sponsor, decide whether to act on this recommendation. Further discussion of these safety tabulations is provided in a specific study protocol.

Sample Size Considerations

Sample size for the study assumed that the number of new stroke events (ischemic or hemorrhagic) would follow a Poisson distribution. The rate of new stroke events was expected to be 0.14 per subject within 3-month after Day 1 in the ASA alone treated group based on a previous study[5]. It was expected that the Clopidogrel/ASA treated group would reduce this by 22%; this is equivalent to 0.11 exacerbations per subject within 3-month after Day 1. With this relative risk reduction, treatment of 32 patients with TIA or minor stroke (regardless of other risk factors) would be expected to rescue one stroke event over 3 months. With a sample size of 5100 patients, we will have 90% power to detect a relative risk reduction of 22% with a two-sided alpha of 0.05, and 5% drop outs (medication non-adherence).

Analysis populations

Total Population

This population will comprise of all subjects screened and for whom a record exists on the study database. This population will be used for listing adverse events occurring prior to randomization and reasons for withdrawal occurring prior to randomization.

Intent-to-Treat Population

The Intent-to-treat (ITT) population will comprise of all subjects Randomized to treatment and who received at least one dose of trial medication. Randomized subjects will be assumed to have received trial medication unless definitive evidence to the contrary exists.
The ITT Population will be used for tables of efficacy, demography, safety, health outcomes, listings of withdrawals after randomization, and all relevant listings. This population will be the primary population for analyses of efficacy and safety.

Per Protocol population

The Per Protocol (PP) population will consist of all subjects in the ITT population not identified as protocol violators. The decision to exclude a subject from the PP population will be made prior to breaking the blind. This population will be used for secondary analyses of the primary efficacy measure. The decision to exclude a subject from the Per Protocol Population will be made prior to breaking the study blind. A partial protocol violator will be included in the Per Protocol Population up to the time of their violation. For the Per Protocol Population, subjects will be analyzed according to the treatment received, providing the same treatment was taken for the duration of the study. If study medication was changed then the subject will be considered a partial protocol violator (from the point of change onwards).

Treatment comparisons

The treatment comparison of interest in this study is between clopidogrel /ASA combination followed by clopidogrel alone regimen and an ASA alone regimen over the 90-day treatment period, based on the ITT population.

General considerations for data analyses

All programming will be performed using SAS Version 9.0. All analysis output will use the following treatment group naming conventions and treatment order:
clopidogrel /ASA for a loading dose of clopidogrel 300mg followed by clopidogrel 75 mg /day day 2-90plus blinded aspirin 75 mg once /day day 2-21 and then aspirin placebo day 22-90
ASA for clopidogrel placebo on day 1, followed by aspirin 75 mg/day plus clopidogrel placebo day 2-90
Unless otherwise specified all significance tests will be 2-sided at the alpha=0.05 level and all confidence intervals will be 95%.

Multicenter Studies

As stated in the protocol, centers with less than 20 subjects will be pooled with larger centers within the same geographic region; this ensures centers are of a reasonable size for the purpose of the statistical analyses. This process will be performed and finalized before the treatment codes are unblinded.

Examination of Subgroups

The rate of new stroke (ischemic or hemorrhagic) and clinical vascular event (ischemic stroke, hemorrhagic stroke, MI, vascular death) at 90 days will be presented for each level of the covariates listed previously. The extent to which the treatment effect varies across levels of each subgroup will be assessed through interaction tests.

Multiple Comparisons and Multiplicity

A single primary efficacy variable has been defined for this study, with all other efficacy variables identified as secondary or other. Similarly only one treatment comparison is of interest in the study and therefore there are no requirements to adjust for multiple comparisons or multiple endpoints within this study.

Data handling conventions

Premature Withdrawal and Missing Data

If any subject withdraws prematurely from the study (prior to the final visit D90±7 days assessment), they are required to complete the withdrawal visit in the CRF. The reasons for withdrawal will be presented in a summary table. For the purposes of summaries and analysis of clinic visit data, this visit will be assigned to the next scheduled clinic visit for that subject, regardless of whether the date falls within the next visit window.

Subjects who withdraw before the end of the study, but who do provide at least one post-baseline measure for a particular endpoint, will be included in the analysis.
Subjects who do not attend any visits after randomization will be excluded from analysis of new stroke and clinical vascular event rates, and safety outcomes, as no post-baseline data will be available.

Event Rates

Summary tables will calculate endpoint event rates (e.g. new stroke, safety outcomes) per 3-month in the following way. The number of 4-week periods that the subject was on treatment for will be rounded up to the next integer. The number of events that a subject had will be divided by the number of 4-week periods, and then multiplied by 3, to give an event rate per 3-month e.g.;

- Number of 4-week periods = round up (number of weeks on treatment / 4)
- Number of event rate per 3-month = 3 × number of events / no of 4-week periods.

For example if a subject had 2 events then withdrew after 3 weeks of treatment

- Number of 4-week periods = round up (3/4) = round up (0.75) = 1
- Number of event rate per 3-mo=3 × (number of events / no of 4-week periods) = 3 × (2 / 1) = 6.

Using 1-month periods in this way means that it is not likely that a subject will have unreasonably high value, which could happen if it was assumed the rate per time was constant. In the example above assuming a constant rate would have lead to a value of 9 events per 3-month, whereas using this method leads to a value of 6 per year.
The average event rate for each treatment group will be calculated as: the sum of number of event for all the patients / the sum of number of 4-week treatment periods for all the patients.

Time to Event Analysis

Differences between treatments in the risk of new stroke (ischemic or hemorrhagic) event and combined vascular events during maximum 90-day follow-up were assessed using standard Kaplan-Meier time-to-event approaches. The time to the first event was used in the model when there were multiple events of the same type. Patients were considered censored at the time of study termination or death if there were no events occurred during the study.

Study Population

Disposition of Subjects

The number of subjects in each analysis population will be presented, subjects to be excluded from the Per Protocol population will be listed, and the total number of subjects attending each clinic visit will also be summarized by treatment group.
The number of subjects Randomized, completed and prematurely withdrawn from the study will be presented for each treatment group. The primary reasons for withdrawal both prior to and post randomization will also be presented.
A data display listing and summary of deviations from the inclusion/exclusion criteria will be presented for all subjects who were either entered or Randomized into the trial.

Protocol Deviations

Subject data will be examined for evidence of protocol violators in order to assess how well the protocol was followed. Inclusion and exclusion criteria are detailed in the study protocol.
Subjects who commit protocol violations will be included in the ITT Population but excluded from the Per Protocol Population. These protocol violations will be shown in a listing. Subjects can either be full or partial protocol violators. A full protocol violator is completely excluded from the Per Protocol Population. A partial protocol violator has only some data excluded. For subjects who violated the protocol during the treatment period due to unpermitted changes in the medication or prohibited concurrent medication, the analysis will only use data recorded prior to the violation.
For all violations which reference the treatment period, the treatment start date will be used as the reference date.
A listing of all possible protocol violators will be produced for clinical review. The final list of subjects who are protocol violators and are therefore excluded from the Per-Protocol population will be agreed by the study team prior to unblinding the study.

Demographic and Baseline Characteristics

The following demographic information will be listed and summarized for subjects in each treatment group: age, sex, body mass index (BMI). This will also be done for smoking history, stroke and TIA history, symptoms of the index event, past medical history, family history, alcohol use, pretreatment Rankin Score and NIHSS score.
Laboratory tests will be listed and summarized for subjects in each treatment group including serum creatinine, glycemia, neutrophil count, and platelet count.
Vital signs including supine systolic blood pressure, diastolic blood pressure, and heart rate will also be listed and summarized in each treatment group.
Qualifying TIA baseline $ABCD^2$ score will be summarized by treatment group.

Treatment Compliance

The overall percentage compliance will be calculated separately for the doses taken for clopidogrel/ASA and ASA alone group using the following formula:

$$\frac{\text{Actual number doses taken}}{\text{Expected number of doses to be taken}} * 100$$

Where expected number of doses taken = [treatment stop date - treatment start date+1].
This data will be listed and summarized for all subjects by treatment group, in addition the number and percent of subjects falling into the following categories will be presented: <20%, 20-<50%, 50-<80% and ≥80%.

Efficacy Analyses

All hypothesis tests for main effects will use a 2-sided test at the 5% level of significance.

Primary Efficacy Analysis

The primary endpoint is the rate of new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period.

Main Model

The time to first new stroke (both ischemic and hemorrhagic) reported during the 3-month treatment period for the ITT Population will be summarized by treatment group using Kaplan-Meier estimates[6]. The hazard ratio for the treatment comparison will be derived using a Cox's proportional hazards model, including the pooled study center as a random effect. The hazards ratios with 95% CI will be reported.
This will also be presented graphically on a Kaplan-Meier plot.

Interactions with Subgroups

Summary tables will be produced for the predefined subgroups and interactions between treatment and these subgroups will be investigated, using a Cox proportional hazard model, with pooled study center as a random effect. A separate model will be used for each interaction to determine its significance.
This will also be presented graphically on a tree plot.

Secondary Efficacy Analyses

Rate of combined vascular events during the 3-month treatment period

The rate of combined vascular events occurring during the treatment will be analyzed using a Cox proportional hazard model similar to that in the previous section, with the pooled study center as a random effect. A combined vascular event was defined as any of the 4 following events: ischemic stroke, hemorrhagic stroke, myocardial infarction, or death from cardiovascular causes. This will also be presented graphically on a Kaplan-Meier plot.
Each of the 4 vascular events will also be analyzed using the same method and the event rate for each event will be calculated for each treatment group.

Death from any causes

The rate of overall death for any cause will be analyzed using a Cox proportional hazard model similar to that in the previous section, with the pooled study center as a random effect. The death rate will be calculated for each treatment group.

Other Efficacy Analyses

Disability measure

Changes of the modified Rankin Scale (mRS) between the end of study and baseline will be summarized for the two treatment groups among the survivors during the study. The treatment difference will be tested using student t-test.

Neurological impairment

Changes of NIHSS scores between the end of study and baseline will be summarized for the two treatment groups among the survivors during the study. The treatment difference will be tested using student t-test.

Quality of life

Health related quality of life will be measured using EuroQol EQ-5D scale among the survivors. Treatment differences will be tested using student t-test.

Time to withdrawal

The time to withdrawal data will be summarized by treatment group, and compared between treatment groups using Kaplan-Meier estimates.
The hazard ratio for the treatment comparison will be derived using a Cox's proportional hazards model, using time to withdrawal as the outcome variable.
This will also be presented graphically on a Kaplan-Meier plot.
In addition, there is potential for differential effects during the early phase of treatment, and thus treatments will also be compared using the Wilcoxon test.

Safety Analyses

All analyses of safety data will be carried out using the ITT population.

Extent of Exposure

The extent of exposure will be calculated as the number of days between start of treatment and end of treatment (i.e. treatment stop date – treatment start date + 1), and categorized into months: <1, 1-2, 2-3 months. Exposure will then be summarized by treatment group.

Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary (Version 6.0 or a later release) and grouped by system organ class (as detailed in the study protocol). Separate data display listings and summaries will be presented for adverse events that start prior to first dose of study medication (pre-treatment), whilst on study medication (during treatment) and after the last dose of study medication (post-treatment).
Within each treatment group, the number and percentage of subjects experiencing an AE will be summarized by system organ class and preferred term and Fisher's Exact test will be used to compare the number of each grouped AE event between treatment groups. In addition, a separate summary will be provided for AEs experienced by more than 5% of subjects in either of the treatment groups.

Deaths and Serious Adverse Events

Summary tables and data displays will be provided for serious adverse events (as detailed in the study protocol). In addition, all deaths and serious AE's will be documented in a case narrative format in the clinical study report.
The number of deaths occurring over the treatment period will be summarized and Fisher's Exact test will

be used to compare the number of deaths between treatment groups.

Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Summary tables will be provided of adverse events leading to discontinuation of study drug and/or withdrawal of the subject.

Pregnancies (as applicable)

Any pregnancies reported during this study will be summarized in case narratives.

REFERENCES

7. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med 1957;J 2(5):200–15.
8. Investigators. TG. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine 1993;329(10):673-82.
9. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.
10. Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. Annals of Medicine 2001;33(5):337-43.
11. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. The Lancet 2007;369(9558):283-92.
12. Andersen P, Gill, RD. Cox's regression model for counting processes: a large sample study. . Annals of Statistics 1982;10:1100-20.

Attachments

Appendix 1: Definition of End Points

Stroke	Sudden symptoms and signs of focal disturbance of cerebral function associated with cerebral circulation disorders. Etiology would be classified based on SSS-TOAST standard.
Ischemic stroke	An acute focal infarction of the brain or retina. Criteria: (1) rapid onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or, (2) rapid worsening of an existing focal neurological deficit that either (a) persists and is not attributable to a non-ischemic etiology (not associated with brain edema, infection, trauma, tumor, seizure, metabolic disease, or degenerative neurological disease) OR (b) is accompanied by evidence of new acute ischemic changes in the brain seen on an imaging study and clearly differentiated from those due to the index ischemic event.
TIA	A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain. Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)
Symptomatic intracerebral hemorrhage	Any extravascular blood in the brain associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Intracerebral hemorrhage is defined as an acute extravasation of blood into the brain parenchyma. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy
Asymptomatic intracerebral hemorrhage	an acute extravasation of blood into the brain parenchyma without clinical deterioration. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy
Other symptomatic intracranial hemorrhage	Any extravascular blood within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy

Other Asymptomatic intracranial hemorrhage	An acute extravasation of blood into the subarachnoid space, epidural space, or subdural space without associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Myocardial infarction with coronary revascularization	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, treated with coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Myocardial infarction without coronary revascularization	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, not treated with coronary revascularization. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.
Coronary Revascularization without myocardial infarction	A procedure to improve coronary blood flow for documented coronary artery disease, but with no documentation of myocardial infarction. Criteria: Documented coronary angioplasty, stenting, or bypass surgery for demonstrated or presumed coronary artery disease
Ischemic vascular death	Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause
Hemorrhagic Vascular death	Death due to intracranial or systemic hemorrhage

Summary of amendments of statistical analysis plan

APPENDIX Ⅰ:

Protocol changes version 1.0 (Jan 20, 2009) to 1.1 (May. 25, 2009)

- ✧ Study objectives (page 4): For Group of clopidogrel plus aspirin, duration of combination of aspirin 75 mg/day is changed from first 30 days into first 21 days.
- ✧ Secondary objectives (page 4): subgroup is added as follows: Time to randomization (<12 hours vs. ≥12 hours)
- ✧ Sample Size Considerations (page 6): 80% statistical power to detect a relative risk reduction of 22% is changed into 90% power while sample size of 3800 is replaced by 5100.
- ✧ Number of Centers: Up to about 80 sites is added to about 100 sites.

Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events(CHANCE)

氯吡格雷用于急性非致残性脑血管事件高危人群的疗效研究

临床研究方案

项目资助单位：中华人民共和国科学技术部

主要研究者：王拥军教授

首都医科大学附属北京天坛医院神经内科

S. Claiborne Johnston, MD, PhD

美国加州大学旧金山分校流行病学、神经病学中心

研究方案版本 1.4

2009-7-25

目录

研究方案签字页

我已经阅读该研究方案，并同意遵守方案要求。

本方案以及所有相关信息的复印件将提供给所有研究人员。我们将一起讨论这些材料，以确保研究员全面地了解研究计划，并保证他们按照 21CFR（Code of Federal Regulations,美国联邦行政法典)的第 50, 54, 56 和 812 部分、ICH-CGP 和伦理委员会要求来完成该研究。

研究中心

_____ _____

中心主要研究者手签名 日期

中心主要研究者打印名

研究方案概要

题目:

比较在 3 个月内使用氯吡格雷，合并在前 21 天内使用阿司匹林与在 3 个月内单独使用阿司匹林治疗急性非致残性脑血管病（TIA 或小卒中）高危人群的安全性与有效性的多中心、随机、双盲、平行对照的临床试验。

主要研究目的:

研究方案为在 TIA/小卒中高危人群中，在 3 个月内联合应用氯吡格雷（起始剂量 300mg，之后 75mg/日）与阿司匹林（75mg/日）治疗 21 天，之后单独应用氯吡格雷（75mg/日），对比在 3 个月内单独应用阿司匹林（75mg/日）的安全性及有效性。首次给药在症状发生 24 小时之内。主要研究目的是评价上述两组研究方案在降低 TIA 和小卒中高危人群的 3 个月卒中（任何类型的卒中，包括缺血性卒中和出血性卒中）风险的差异。

研究设计:

该项研究为多中心、随机、双盲、双模拟临床试验。主要无效假设为在中高危 TIA 和小卒中患者症状出现 24 小时内使用 3 个月氯吡格雷（起始剂量 300mg）合并前 21 天使用阿司匹林（75mg/日）与单独使用阿司匹林（75mg/日）3 个月随访时发生主要终点事件(缺血性卒中和出血性卒中)的风险无差异。

研究人群：

年龄≥40 岁的中高危卒中风险（随机化时 ABCD2 评分≥4）的 TIA（局灶性脑或视网膜缺血导致的神经功能障碍，并在 24 小时内完全消失）或急性非致残性缺血性卒中患者（随机化时 NIHSS≤3 分），且在症状出现的 24 小时内可以应用研究药物。症状开始的时间定义为“最后看起来正常的时间”。

入组标准：

- 年龄≥40 岁。
- 急性非致残性缺血性卒中（随机化时 NIHSS≤3 分），且在症状出现的 24 小时内可以应用研究药物。症状开始的时间定义为“最后看起来正常的时间”
- 具有中高危卒中风险（随机化时 ABCD2 评分≥4）的 TIA（局灶性脑或视网膜缺血导致的神经功能障碍，并在 24 小时内完全消失）患者，且在症状出现的 24 小时内可以应用研究药物。症状开始的时间定义为“最后看起来正常的时间”。
- 已签署知情同意书

排除标准：

- 根据基线头 CT 或 MRI 诊断为出血或其他病理性脑疾患，例如血管畸形、肿瘤、脓肿或其他常见的非缺血性脑疾病（例如多发性硬化）。

- 仅存在单独的感觉症状（如麻木感），单独的视力改变，单独的头晕或眩晕，但基线头 CT 或 MRI 没有急性梗死证据。
- 随机化时 mRS>2 分（发病前的病史评估）。
- 随机化时 NIHSS≥4 分。
- 具有明确的抗凝治疗指征（怀疑存在心源性栓塞，如房颤、已知的人工心脏瓣膜、可疑的心内膜炎等）。
- 存在使用氯吡格雷或阿司匹林的禁忌症：.
- 已知过敏史；
- 严重的肝功能不全或肾功能不全；

备注：严重的肝功能不全是指 ALT 值>2 倍正常上限或 AST 值>2 倍正常上限；严重的肾功能不全是指肌酐值>1.5 倍正常上限。

- 严重的心功能衰竭、哮喘；
- 存在凝血障碍、系统性出血；
- 既往凝血障碍或系统性出血病史；
- 既往血小板减少或中性粒细胞减少病史；
- 既往有药物引起的血液系统疾病或肝功能异常史；
- 白细胞减少(<2×109/l)或血小板减少(<100×109/l)；
- 随机化前 24 小时内使用过溶栓药物。

- 颅内出血病史
- 预计需要长期服用非研究性抗血小板聚集药物，或影响血小板功能的非甾体类抗炎药物。
- 随机化前十天内使用过肝素或口服抗凝药物。
- 随机化前三个月内有胃肠道出血或大手术。
- 血管成形术或血管外科手术导致的 TIA 或小卒中。
- 计划中的其他外科手术或介入性治疗可能需要终止服用试验药物。
- 血管成形术或血管外科手术导致的 TIA 或小卒中。
- 患有严重非心血管疾病，预期生存时间小于 3 个月的患者。
- 没有采取有效的避孕措施且妊娠试验阳性记录的育龄期女性。
- 正在接受试验性药物或仪器试验的患者。

随机化： 随机码列表将在合同研究组织（CRO）集中生成。

患者的药物将按照随机码表进行包装。在治疗期间，患者将接受氯吡格雷/阿司匹林组或者阿司匹林组的研究药物治疗，分配到两组的随机概率为 1:1。

在研究第 1 天（基线访视）时，研究治疗号将由中心化的互动语音电话系统（Inter-voice Response System, IVRS）分配。在患者进行随机化之前，分中心研究者必须拨打 IVRS，提供患者信息（例如研究号，患者出生日期和姓名缩写，分中心，随机化距症状发生时间）。随后，研究者将获得研究治疗号，并分发给患者相应的第一盒研究用药。

主要有效性终点事件： 3个月内新发任何卒中事件（缺血性卒中或出血性卒中）

研究周期： 每个受试者随机化后完成 90 天随访；整个试验将花 3 年时间完成。

预计中心数： 在全国临床研究网络中筛选 100 余家中心

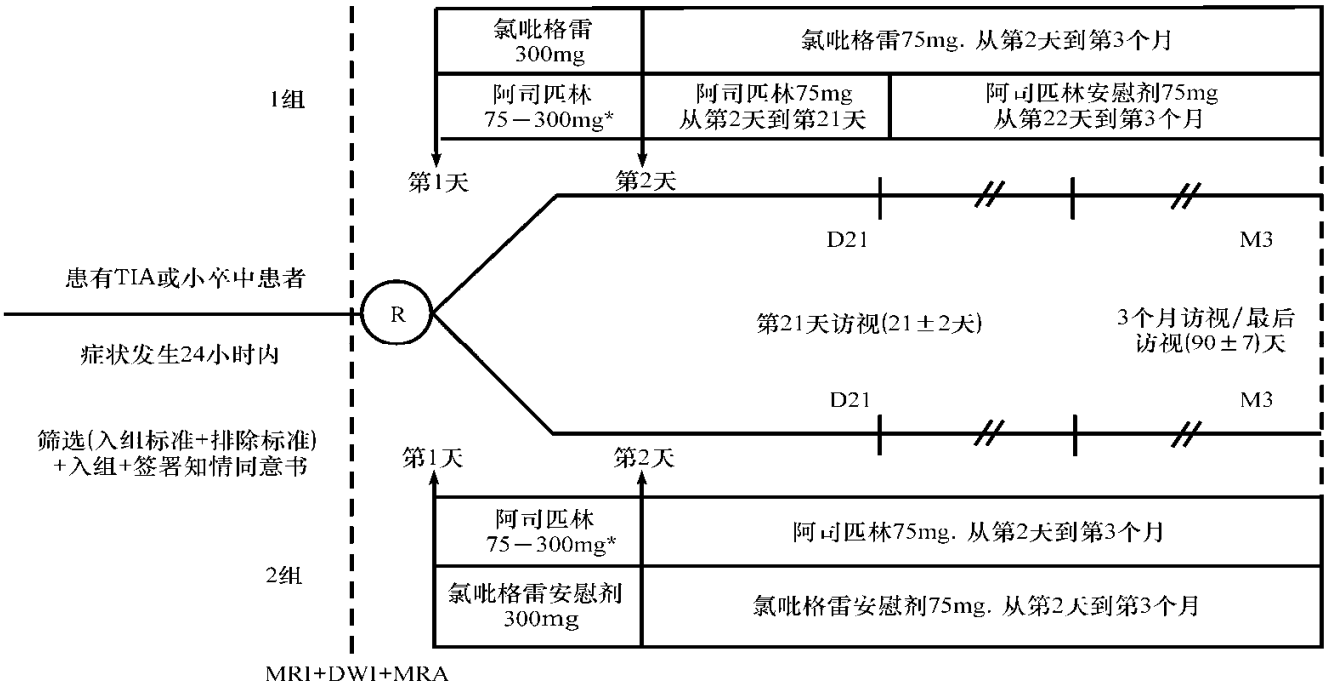
样本量： 总样本量 5100 例受试者

统计分析： 对于 ITT 数据集中两组治疗方案，都采用了 Kaplan-Meier 方法来估计 3 个月治疗期内的新发首例卒中(包括缺血和出血性卒中)的时间。此外，采用 Cox 比例风险模型计算两种治疗方案间的风险比(HR 值)，模型

中设定中心效应为随机效应. 风险比(HR 值)将报告 95%可信区间。

3 研究流程

1.1 研究设计图



*在第 1 天给予阿司匹林的总剂量(75mg-300mg)包括在第 1 天内任何时间、任何地点（包括在急诊室）给予患者的阿司匹林。

图 1 CHANCE 研究设计图

1.2 研究流程图/表

措施	筛选及入组	治疗期			
		第 1 天	第 21±2 天	第 90±7 天（终点访视）	终点事件访视
人口统计学特征	X				
mRS	X		X	X	X
NIHSS	X		X	X	X
ABCD^{2}评分(仅 TIA)	X				
本次发病症状	X				
体格检查	X		X	X	X
既往病史	X				
当前药物治疗	X		X	X	X
头 CT/MRI	X*				
实验室检查**	X*				X
心电图	X*				X
核实入组/排除标准	X				
签署知情同意书	X				
随机化	X				
头核磁共振	X***			X***	X
留血		X****			
认知评估(MoCA)		X*****		X	
EQ-5D 量表				X	
给予第 1 次治疗		X			
给予第 2 次治疗			X		
不良事件/严重不良事件			X	X	X
治疗依从性			X	X	X

* 标准评估：基线期费用将不包括在研究中。

** 包括：血常规（包括白细胞计数、中性粒细胞计数、血红蛋白、血小板计数等）、凝血象、空腹血糖、肝肾功能（包括血肌酐，血清转氨酶等）。

*** 包括 T1+T2+DWI+FLAIR+T2*+MRA 序列。仅参与影像学亚组研究的患者需要完成。根据各分中心情况，可以在随机化前完成，也可以在随机化后完成。

**** 仅参与病因学亚组研究的患者需要留取。在随机化后尽快完成。

***** 在随机化后 48 小时内尽快完成。

2 研究背景

2.1 中国急性非致残性脑血管事件的疾病负担

中国是世界上脑血管病负担最大的国家，不仅因为其人口基数庞大，而且中国人群更易罹患脑血管疾病；死于脑

血管疾病的患者数量高达死于心血管疾病的 3 倍[1, 2]。

急性非致残性脑血管事件包括：短暂性脑缺血发作（TIA），其症状持续小于 24 小时；以及急性缺血性小卒中，定义为一种 NIHSS≤3 的缺血性卒中，它通常是致残性卒中的先兆。缺血性脑血管事件包括缺血性卒中和短暂性脑缺血发作，是主要的脑血管疾病亚型。在中国，估计每年有超过 200 万的新发卒中事件发生[1, 3]，研究显示其中大约有 65%为脑缺血事件，在这些脑缺血事件中大于 10%的患者为缺血性小卒中(数据源于急性脑血管事件登记研究，是全国性的，以医院为基础的登记研究，数据尚未发表)。迄今为止在中国还没有关于 TIA 发病率的报道。在美国每年 TIA 的发病率大约为 68/100,000 至 86/100,000，大约每年有 300,000 人被诊断为 TIA[4-7]。基于美国流行病学调查研究，估计中国每年大约有将近 100 万人被诊断为新发 TIA。令人们更为担心的是，自从 20 世纪末以来，西方国家卒中的发病率和死亡率逐年降低，然而在中国缺血性卒中的发病率与死亡率却逐年增长，并成为国民健康的第一杀手[2, 8-11]。

对于非致残性脑血管病患者而言，早期卒中或其他血管事件复发是最令人沮丧的医疗情况之一[12, 13]。一些调查研究表明：即使对于那些采用标准阿司匹林治疗的患者而言，TIA 和缺血性小卒中早期（3 个月）发生致残性卒中的风险也远高于预期[14-18]。虽然受人群和医院设施的差异性限制，仍有研究表明在 TIA 和缺血性小卒中发生 90 天后发生卒中的危险性高达 10%-20%[14, 15, 18-23]。

2.2 急性非致残性脑血管事件的治疗

对于急性非致残性缺血性脑血管事件，很少有确定的，有效的治疗或预防药物。除了阿司匹林外，唯一被认可的药物是静脉注射的组织纤维蛋白溶酶原激活剂(tPA)[24]。然而，tPA 仅针对症状发生在 3 小时内的患者。患者不适合溶栓的最常见原因是症状逐渐改善或症状太轻而不能保证治疗效果，以及到医院的时间超过了可以使用 tPA 的 3 小时时间窗[25]。因此，对于大多数急性非致残性脑血管事件患者而言尚无有效的急性期治疗措施。

血小板聚集是脑缺血的一个重要作用因素，在其它部位的局部缺血也是一样。目前，对于各种不同的病理生理亚型（包括心源性、小血管卒中、大血管卒中等）抗血小板聚集治疗均可在不同程度上降低卒中发生的风险[26-28]。

2.2.1 阿司匹林

目前为止，阿司匹林是唯一经过研究证实有效的用于脑血管事件患者急性期的抗血小板药物，但是其疗效有限，且疗效被轻度增加的颅内出血风险部分抵消。 CAST 和 IST 两个研究招募大约 20000 名缺血性卒中患者治疗 2-4 周，使用阿司匹林用于急性期治疗可降低缺血性卒中复发的风险达 30%(绝对的变化为 0.7%)，同时伴有一小部分增加颅内出血的风险(相对增加 25%，绝对增加 0.2%)[29-31]。因此，阿司匹林已经成为卒中急性期治疗的标准用药。关于阿司匹林的最佳剂量一直存在激烈的争论，每天使用剂量范围大概在 50-325mg 之间[32]。对于 TIA 患者，阿司匹林也被认为是标准的治疗，氯吡格雷和阿司匹林-双嘧达莫联合制剂也是替代方案，但是尚无试验证实它们可以用于急性期治疗[33-36]。

2.2.2 双嘧达莫

两个临床试验已经证明在预防卒中复发方面双嘧达莫是有效的，这两个试验分别是：ESPRIT[37]和 ESPS-II[38]。试验同时证明双嘧达莫和阿司匹林合用的疗效优于单独使用阿司匹林的疗效。在 ESPRIT 试验中，双嘧达莫与阿司匹林联合应用，结果显示出血的风险没有增加。但目前仍没有评估在卒中或 TIA 的急性期联合应用双嘧达莫/阿司匹林的临床试验（上述两个试验平均入组时间大于 1 个月），所以在发病 1 月内药物的安全性和有效性尚不得而知。

PROFESS 试验[39, 40]没有达到阿司匹林/缓释双嘧达莫对照氯吡格雷预设定的非劣性检验标准，阿司匹林/缓释双嘧达莫联用组和氯吡格雷组在卒中和其他主要血管事件复发上有相似的比率。主要的出血性事件包括：颅内出血在使用阿司匹林/缓释双嘧达莫中更常见，但是绝对风险降低，且被更少的缺血事件部分抵消。在中国，阿司匹林/缓释双嘧达莫尚未得到 SFDA 的批准。因此，在临床实践中，阿司匹林和氯吡格雷合用是对于卒中高危人群或急性期的唯一可能的联用策略。

2.2.3 氯吡格雷

氯吡格雷为噻吩吡啶衍生物，通过阻断二磷酸腺苷受体[41-43]抑制血小板聚集，并不作用于被阿司匹林抑制的血栓素介导途径。CAPRIE 试验中，氯吡格雷 75mg/日使卒中、心肌梗死或血管性死亡的长期风险降低 8.7%，相对于使用阿

司匹林的心血管疾病患者没有增加出血的风险或其它主要的副作用[44]。这个试验没有设计评价氯吡格雷在卒中急性期治疗中的作用，同时没有试验评价 TIA 或小卒中患者中使用氯吡格雷的有效性。

氯吡格雷在血管事件后作为急性期治疗具有潜在临床治疗基础。氯吡格雷起始剂量 300mg 将产生血小板抑制作用，并在 2 小时内达到稳态水平[45, 46]。

2.2.4 联合应用氯吡格雷/阿司匹林

已经有几个血管病试验研究了氯吡格雷联合应用阿司匹林的疗效，其中有两个试验包括了卒中或 TIA 患者。尽管这些试验的结果并不支持在卒中和 TIA 后长期应用氯吡格雷，但这些试验并未检验在该人群中氯吡格雷作为急性期治疗的效果，同时这些试验支持在小卒中或 TIA 后使用氯吡格雷可能收益更大，更加安全。

阿司匹林和氯吡格雷具有协同抗血小板聚集作用[44, 47-49]，在卒中预防中联合使用可能增加收益。阿司匹林和氯吡格雷已联合应用于冠状动脉、颈动脉、及颅内动脉支架术，并具耐受性[50, 51]。同样，来自心脏临床试验、非急性卒中/TIA 试验，以及最重要的 TIA 和小卒中的急性预试验均支持氯吡格雷与阿司匹林联合应用的价值，如下所述。

2.2.4.1 心血管临床试验

CURE 试验表明在急性冠脉综合征人群中在服用阿司匹林同时使用氯吡格雷起始剂量 300mg 继而 75mg/日，3 个月随访结束时阿司匹林联用氯吡格雷组可降低卒中、心肌梗死、血管性死亡的风险达 20%，这种疗效在前 10 天内尤为明显[52]。该试验终点事件中心肌梗死和血管性死亡占了较大比例。阿司匹林联用氯吡格雷组重大出血事件的风险略有增加，但致命性出血事件的风险与对照组并无差异。在 CREDO 研究中，对于那些经皮冠脉介入术后使用阿司匹林的患者中，同时使用氯吡格雷使 1 年心血管事件风险降低 27%[53]。早期获益仅在那些在介入操作前≥6 小时内接受了起始剂量氯吡格雷的患者中看到，这可能提示在缺血事件发生数小时内服用起始剂量的重要性。在术后 28 天时重大出血风险绝对增加 1%，但这些出血事件多数与临床操作相关，例如搭桥手术。因此，氯吡格雷与阿司匹林联用能减少急性期冠状动脉缺血事件发生率或在经皮冠状动脉介入手术前的缺血事件发生率。

2.2.4.2 非急性期卒中/TIA 临床试验

MATCH 试验是一项卒中二级预防试验，入组 7599 例患者，主要为欧洲患者[54]。该研究比较阿司匹林联合应用氯吡格雷与单独应用氯吡格雷的疗效差异。入组的大多数患者（79%）为卒中患者而非 TIA 患者。试验总体结果是阴性的，在减少缺血事件方面有 1%的绝对获益，但被绝对增加的 1%的重大出血事件风险所抵消。然而，在亚组分析中，那些在确诊卒中或 TIA 后立即接受治疗的患者有获益增加的趋势，在 7 天之内接受治疗的患者相对危险度（RR）降低 17%。CHARISMA 试验随机入组患有血管病的患者，阿司匹林 75-162mg/日治疗组对比氯吡格雷 75mg/日治疗组以及安慰剂组[55]。与 MATCH 试验类似，该试验结果为阴性，减少缺血事件的疗效被少量的严重出血所抵消。但是，同样与 MATCH 试验类似的是，那些在确定临床事件（包括卒中和 TIA）后立即接受治疗的患者更能获益。CHARISMA 试验（数据未发表）入组 4320 例 TIA 或卒中患者，主要研究者为 Dr. Johnston 和 Dr. Easton。研究表明，在卒中后 30 天内随机入组的患者中使用氯吡格雷治疗相对危险度降低 26%，而在 30 天之后随机入组的患者其相对危险度降低 17%，这再次表明早期接受治疗的患者更有可能获益。在 30 天之内或之后接受治疗的随机化入组的卒中或 TIA 患者出血风险并无增加。

2.2.4.3 急性 TIA/卒中预试验

FASTER 试验[56]使用析因设计评价了在使用阿司匹林的基础上在 TIA 或小卒中发生后 24 小时内同时使用氯吡格雷（起始剂量 300mg，之后 75mg/日）及辛伐他汀的疗效。该试验的主要意义是认识到表现为急性缺血性卒中而不符合溶栓标准的患者预后差非常常见。该试验有 18 个分中心参与，在 30 个月内入组了 392 例患者。单独使用阿司匹林的患者 90 天卒中（缺血性或出血性）风险为 11%，联合使用氯吡格雷/阿司匹林的患者 90 天卒中风险为 7%，优势比为 36%，无显著性差异（p=0.19）。该试验共出现 2 例颅内出血，两位患者均使用氯吡格雷联合阿司匹林治疗：1 例为小卒中患者，其血压控制不良；另 1 例为 TIA 患者，但细节不详。这些出血事件包括在主要终点事件中，并不抵消联合使用氯吡格雷/阿司匹林带来的收益。对计划进行的试验而言，该试验是优秀的试点试验，它再次确定了 TIA 和小卒中患者具有较高的卒中风险，并且表明联用氯吡格雷/阿司匹林可能存在更大收益。

另外一个双盲、安慰剂对照的试点试验（CARESS），评价在 107 例症状性颈动脉狭窄患者中联合应用氯吡格雷/阿司匹林对比单独应用阿司匹林在 TCD 微栓子信号方面的差异[57]。在 7 天内 44%的联合应用组患者以及 73%的阿司匹林

组患者出现持续性微栓子信号（p=0.005），这表明联合应用氯吡格雷/阿司匹林能够降低可能发生的血栓栓塞风险。单独应用阿司匹林组比联合应用组卒中和 TIA 发生几率更高（11：4），但差异并无显著意义。

2.2.4.4 重大出血事件的风险

尽管非急性卒中或 TIA 的试验表明联合应用氯吡格雷/阿司匹林增加重大出血事件的风险，但在 TIA 或小卒中后急性期内栓塞的风险极高，且与中等或严重卒中相比预期出血风险较低，因此在这种情况下联合应用氯吡格雷/阿司匹林可能更有效，相对更安全。事实上，TIA 或小卒中患者仅有微小梗死灶或无梗死灶，因此其出血风险可能更接近于仅有心脏疾患的患者，而不是那些完全卒中患者（残疾程度满足之前试验入组标准）[58]。例如，在 TOAST 研究中，使用肝素类药物的 NIHSS＞15 的患者严重脑出血的风险为 14%，而那些非严重卒中患者的风险仅为 0.5%[59]。因此，在 TIA 或小卒中患者中联合使用氯吡格雷/阿司匹林的出血风险应相对较低。

2.3 结论

TIA 或小卒中处于一种易被公众和医生忽视的状态。许多研究表明 TIA 和小卒中在短期内发生卒中的风险高于完全性卒中。如果在发病初期对 TIA 和小卒中立即采取有效治疗，那么将显著降低其整体卒中负担。在这种急性病理生理状态中抗血小板治疗可能担当重大角色。然而，还没有大规模的试验对 TIA 或小卒中进行急性期干预的评价。

FASTER试验和其它在发生TIA或小卒中之后联合应用氯吡格雷和阿司匹林的阴性试验均表明在发生TIA或小卒中后立即开始氯吡格雷和阿司匹林联合的治疗可能是有益的。因为这些数据来源于规模较小的预试验研究和亚组分析，尚不能作为临床应用的证据。但它们对TIA和小卒中后进行强化抗血小板治疗的大规模临床试验提供了强有力的支持[60]。总之，考虑到上述数据以及TIA或小卒中患者具有发生血管性事件的高度风险（尤其是在急性期），本研究提议的设计预期能使患者在获得最大获益的同时使出血事件风险最小。

3 研究目的

3.1 主要研究目的

该临床试验为随机、双盲、多中心研究。研究方案为在 TIA/小卒中高危人群中，在 3 个月内联合应用氯吡格雷（起始剂量 300mg，之后 75mg/日）与阿司匹林（75mg/日）治疗 21 天，之后单独应用氯吡格雷（75mg/日），对比在 3 个月内单独应用阿司匹林（75mg/日）的安全性及有效性。首次给药在症状发生 24 小时之内。主要研究目的是评价上述两组研究方案在降低 TIA 和小卒中高危人群的 3 个月卒中（任何类型的卒中，包括缺血性卒中和出血性卒中）风险的差异。

3.2 次要研究目的

3.2.1. 评估次要复合终点事件：由任何类型的卒中、心肌梗死以及血管性死亡组成。

3.2.2. 评估符合研究方案的目标人群的主要终点事件。目标人群包括无明显中断服药的患者（实际服药剂量小于预期总量的 80%）和未重大违反研究方案的患者。

3.2.3. 分别评价联合应用氯吡格雷/阿司匹林组与单独应用阿司匹林组在下列终点事件发生率上的疗效差异：缺血性卒中、出血性卒中、短暂性脑缺血发作、心肌梗死、血管性死亡。

3.2.4. 评价 mRS 的连续性变化和最后一次随访时 mRS 为 0-2 分的患者的比例。

3.2.5. 比较两种治疗方案对下列事件的安全性差异：

✧ 严重或中度出血（GUSTO 定义，见附表）；

✧ 颅内出血；

✧ 总体死亡率；

✧ 不良事件/严重不良事件

- 血栓性血小板减少性紫癜(TTP)
- 粒细胞减少
- 超敏反应
- 肾衰竭

3.2.6. 比较在不同病因学分型（非颅内大血管疾病对比颅内大血管疾病）中两种治疗方案的有效性和安全性差异。

3.2.7. 比较在不同目标事件（TIA 对比小卒中）中两种治疗方案的有效性和安全性差异。

3.2.8. 对于那些发病前曾服用阿司匹林和/或氯吡格雷的患者，比较两种治疗方案对他们的有效性和安全性差异。

3.2.9. 比较在不同性别和年龄（<65 岁对比≥65 岁）患者中两种治疗方案的有效性和安全性差异。

3.2.10. 在更多的探索性分析中，评价存活者神经功能残损(NIHSS 评分的改变)，认知功能(蒙特利尔认知评估（MoCA）)，和生活质量(EQ-5D 量表)。

3.2.11. 比较不同随机化时间（小于 12 小时对比大于 12 小时）两种治疗方案的有效性和安全性差异。

3.2.12. 评估有或没有最初头 CT 或 MRI 影像梗死的证据患者的主要终点事件和颅内出血事件的发生率。

4 研究设计和管理概述

4.1 研究设计概述

该随机、双盲多中心临床试验的主要无效假设为在 TIA 和小卒中患者症状出现 24 小时内使用 3 个月氯吡格雷（起始剂量 300mg）合并前 21 天使用阿司匹林（75mg/日）与单独使用阿司匹林（75mg/日）90 天随访时发生主要终点事件(缺血性卒中和出血性卒中)的风险无差异。

中高危 TIA 患者（随机化时 ABCD^{2}评分≥4）和急性非致残性缺血性卒中患者（随机化时 NIHSS≤3 分）必须随机分

组，并在症状出现的 24 小时内给予首剂研究药物。患者将被随机分为两组：

第一组：	随机化第 1 天	氯吡格雷 300mg+阿司匹林 75-300mg（标签公开）
	第 2 天至 21 天	氯吡格雷 75mg/日+阿司匹林 75mg/日
	第 22 天至 3 个月	氯吡格雷 75mg/日+阿司匹林安慰剂
第二组：	第 1 天	氯吡格雷安慰剂+阿司匹林 75-300mg（标签公开）
	第 2 天至 3 个月	氯吡格雷安慰剂+阿司匹林 75mg/日

评估两组患者在 90 天随访中发生的任何新发卒中风险（缺血性卒中和出血性卒中）。

该研究预计在全国 100 家临床研究网络和 CHANCE 研究临床协作单位开展，招募 5100 例受试者，在 35 个月内完成该研究。数据安全监测委员会（DSMB）将定期监督本研究的安全与进展。

4.2 研究时间表

建立了 1 个 3 年研究预算与招募计划，主要研究时间节点如下：

研究时间表

注册之前-研究开始	9 个月(2009.01-2009.09)
招募和随访	19 个月 (2009.10- 2011.04)
随访完成	3 个月 (2011.05-2011.07)
数据分析与文章发表	4 个月 (2011.08-2011.11)
总时间	35 个月

*研究持续时间(每个患者)=3 个月

4.3 研究组织

主要研究者：

王拥军教授，中国首都医科大学附属北京天坛医院神经内科。

Claiborne Johnston 教授，美国加州大学旧金山分校神经病学、流行病学中心。

CHANCE 筹划指导委员会成员：

王拥军教授

Claiborne Johnston 教授(美国- 共同第一负责人 PI)

L. Wong 教授(香港)

David Wang 教授 (美国)

James Wang 教授 (美国)

Mai N. Nguyen-Huynh 教授 (美国)

王晨教授

崔丽英教授

李焰生教授

董强教授

徐剑锋教授

贾建平教授

吴江教授

曾进胜教授

赵性泉教授

刘丽萍教授

王春雪教授

王伊龙教授

- 筹划指导委员会将对试验进行科学性和战略性的指导，并且对试验的设计、执行和发表全权负责。
- 筹划指导委员会将确保研究质量、研究的执行和管理。
- 筹划指导委员会将在研究开始前批准研究方案和操作指南。
- 筹划指导委员会将定期召开电话会议或面对面会议以讨论和汇报研究的进展。
- 筹划指导委员会的组成及其职责在执照中描述，其最终形式将在试验开始前确定。

执行委员会

执行委员会由 2 位主席及筹划指导委员会的其他成员组成，包括 2 个项目经理，将是执行委员会的成员。他们将召开密集的会议（电话会议或现场会议）来评审试验进展情况及收集可用的盲态数据，并对研究进行适当的指导。

主要决定将由执行委员会组织面对面会议决策。

执行委员会的组成职责及其职责在执照中描述，其最终形式将在试验开始前确定。

执行委员会成员：王拥军，Claiborne Johnston（美国），王伊龙，赵性泉，刘丽萍，孟霞，王安心，林金嬉

数据安全监测委员会

数据安全监测委员会(DSMB)将定期监督本研究的进展，以确保 CHANCE 研究达到道德规范和患者安全的最高标准。

它由学术成员组成，包括独立的统计学家，他们不单独参与试验。DSMB 资格将在试验开始前经由 DSMB 和执行委员会证明，包括会员资格、角色、职责。

每一次 DSMB 会议后，报告将立即上交给委员会主席。

数据安全监测委员会（DSMB）成员：李昊，沈海鹏，王伊龙，王安心，刘改芬，王献伟，潘岳松

裁决委员会

临床终点事件（卒中、心肌梗死、死亡、大出血）将由试验之外的专家（神经科专家、心脏病专家）进行复审。裁决委员会成员资格（包括资格、角色、职责）应在试验开始之前经由裁决委员会和执行委员会认证。

与临床相关事件的神经影像将首先在分中心阅读，在裁定文件中将包括影像报告。在特殊情况下，裁决委员会可能将要求分中心或中心实验室递交原始影像文件。

裁决委员会成员：Lawrence. Wong（香港），David Wang（美国），James Wang（美国），李焰生，徐安定，高培毅

4.4 中心培训，认证

执行委员会对所有分中心进行了 GCP 培训以及结局评价的培训（例如:NIHSS,mRS）

在研究启动之前，分中心主要研究者和协调员按照要求完成培训并取得认证证书。在这些培训项目中，研究者对患者进行筛选的标准和随访的过程将被评估。在案例研究过程中一些涉及研究方案的潜在问题或模糊不清的内容将被讨论。

所有的研究者必须完成以下的培训并取得证书：

- 研究流程
- TIA 的诊断方法的指导说明
- ABCD2 的使用

- CHANCE 的入组条件
- mRS 评分
- NIHSS 评分
- SSS-TOAST
- EQ-5D
- 终点事件判读
- GUSTO
- 血样亚组的血样收集
- 影像亚组影像学资料收集（DICOM 格式）

每个中心在招募患者之前必须要完成项目培训并获得认证。研究中心 PI 和主要研究成员将定期参加电话会议以解决研究中遇到的问题。认证资格将由 4 个培训中心颁发。

详尽的研究流程手册作为研究者的主要参考文档。它为研究中心的研究者提供培训指导，并在整个研究期间定期地根据需要在 CHANCE 研究网站上进行更新。执行委员会成员与研究协调员将以电话，传真或 e-mail 的形式与中心研究者保持沟通，解决研究中遇到的问题。CHANCE 执行委员会与监督委员会一起回答各分中心遇到或提出的疑问，并将这些疑问和答案整理后分发给所有分中心。并保证这些疑问和答案在 CHANCE 研究网站上可以获得。

执行委员会成员将管理并实地考察分中心，以确保记录在病例报告表中的数据的完整性与有效性。在整个试验过程中每个研究中心至少被考察一次，如果研究数据质量有疑问或受试者入组有问题会根据需要增加考察次数。

4.5 访视计划

受试者访视时间包括筛选，随机化，21 天访视，90 天访视。除外，患者出现新神经系统临床症状，可疑事件发生

时将接受访视，包括原缺血事件恶化，出现新的短暂的或持续的神经系统症状。分中心将在事件发生 72 小时内将提交事件判读资料。

4.6 结局

对于终点事件结局的定义在附件 1 已给出

4.6.1 主要有效终点

3 个月内新发血管性事件患者的比例，定义为如下任何事件：

- ✧ 任何卒中事件（缺血性或出血性卒中）

4.6.2 次要有效终点

- 3 个月内的血管性事件患者的比例（卒中，心肌梗死，血管性死亡）
- 3 个月内新发血管性事件患者的比例（缺血性卒中/出血性卒中/TIA/心肌梗死/血管性死亡），将其作为一组评估或分别评估。
- mRS 的改变（连续性）和在 3 个月随访时评分为 0-2 分对比 3-6 分两组百分比的改变（量表见附件 2）
- 进一步的针对有效性探索分析：
  - ✧ 神经功能残损(在 3 个月随访时 NIHSS 评分的改变)（量表见附件 3）；
  - ✧ 生活质量(EQ-5D 量表)（量表见附件 4）
- 也将对有效终点事件进行病因学亚组分层分析(非颅内大动脉狭窄性疾病对比颅内大动脉狭窄性疾病)，目标事件（TIA 对比小卒中）分析，年龄分析（<65 岁对比≥65 岁）

4.6.3 安全性终点事件

4.6.3 .1 临床安全性

评价临床安全性，如下：

- ✧ 在第 1 天、第 21 天和第 3 个月访视时进行体格检查，包括神经系统评估检查；
- ✧ 基线期后每次访视时收集不良事件信息；
- ✧ 每次访视时测量卧位血压和心率。

4.6.3 .2 不良事件的收集

在本研究期间不需要特殊的实验室检查。然而，如果实验室检查结果异常与研究药物相关或导致需要上报的不良事件，那么要求采取特殊的、恰当的行动（见附件 5）

4.6.3 .3 心电图

在基线期随访（第 1 天）应做心电图

4.6.3 .4 安全性终点事件

4.6.3.4.1 主要安全性终点事件

- ✧ 严重出血事件发生率(GUSTO 定义，见附件 6)，包括致命性出血和症状性颅内出血；

4.6.3.4.1 次要安全性终点事件

- ✧ 3 个月时症状性和非症状性颅内出血的发生率
- ✧ 总体死亡率
- ✧ 研究者报告的不良事件/严重不良事件

5 患者筛选

在整个研究期间，100 家分中心拟入组 5100 例 TIA 或小卒中受试者。在患者招募之前，所有的分中心都必须获得当地伦理委员会的批准，伦理委员会可获取所有研究文档和培训材料。

5.3 研究人群

入选标准

- 年龄≥40 岁。
- 急性非致残性缺血性卒中（随机化时 NIHSS≤3 分），且在症状出现的 24 小时内可以应用研究药物。症状开始的时间定义为“最后看起来正常的时间”。
- 具有中高危卒中风险（随机化时 ABCD^2 评分≥4）的 TIA（局灶性脑或视网膜缺血导致的神经功能障碍，并在 24 小时内完全消失）患者，且在症状出现的 24 小时内可以应用研究药物。症状开始的时间定义为“最后看起来正常的时间”。
- 已签署知情同意书。

排除标准

- 根据基线头 CT 或 MRI 诊断为出血或其他病理性脑疾患，例如血管畸形、肿瘤、脓肿或其他常见的非缺血性脑疾病（例如多发性硬化）。
- 仅存在单独的感觉症状（如麻木感），单独的视力改变，单独的头晕或眩晕，但基线头 CT 或 MRI 没有急性梗死证据。
- 随机化时 mRS>2 分（发病前的病史评估）。
- 随机化时 NIHSS≥4 分。

- 具有明确的抗凝治疗指征（怀疑存在心源性栓塞，如房颤、已知的人工心脏瓣膜、可疑的心内膜炎等）。
- 存在使用氯吡格雷或阿司匹林的禁忌症：
  - 已知过敏史；
  - 严重的肝功能不全或肾功能不全；
  - 严重的心功能衰竭、哮喘；
  - 存在凝血障碍、系统性出血；
  - 既往凝血障碍或系统性出血病史；
  - 既往血小板减少或中性粒细胞减少病史；
  - 既往有药物引起的血液系统疾病或肝功能异常史；
  - 白细胞减少（$<2\times10^9/l$）或血小板减少（$<100\times10^9/l$）；
  - 随机化前 24 小时内使用过溶栓药物。
- 颅内出血病史
- 预计需要长期服用非研究性抗血小板聚集药物，或影响血小板功能的非甾体类抗炎药物。
- 随机化前十天内使用过肝素或口服抗凝药物。
- 随机化前三个月内有胃肠道出血或大手术。
- 随机化后三个月内计划或很可能行血管成形术或血管外科手术。
- 计划中的其他外科手术或介入性治疗可能需要终止服用试验药物。

- 血管成形术或血管外科手术导致的 TIA 或小卒中。
- 患有严重非心血管疾病，预期生存时间小于 3 个月的患者。
- 没有采取有效的避孕措施且妊娠试验阳性记录的育龄期女性。
- 正在接受试验性药物或仪器试验的患者。

6 治疗方案

6.1 研究药物

本随机、双盲研究的主要目的是比较氯吡格雷与阿司匹林联合应用，之后单独应用氯吡格雷组与单独使用阿司匹林组疗效的差异。研究使用的两种氯吡格雷片剂(75mg 有效的氯吡格雷和氯吡格雷安慰剂)是难以辨别的(其大小、形状、颜色、外观完全相同)。

在本研究中，药物的轻微副作用是不常见的，因此，受试者或研究者不可能通过副作用来区分安慰剂与活性药物。而且分中心使用的生物学实验没有揭盲的可能。

研究者不能揭盲随机码（治疗码），除非出现特殊情况。例如，发生严重不良事件（SAE）时，公开研究药物信息对治疗受试者非常重要的情况下，才可以揭盲研究药物。

6.2 药品规格

- ✧ 氯吡格雷，每片 75mg；
- ✧ 氯吡格雷安慰剂，每片 75mg
- ✧ 阿司匹林，每片 75mg；
- ✧ 阿司匹林安慰剂，每片 75mg。

6.3 给药方式

- ✧ 口服

6.4 剂量方案

第一组：

- ✧ 第 1 天*：氯吡格雷 300mg 和公开标签的阿司匹林 75mg-300mg。
- ✧ 从第 2 天到第 21±2 天：氯吡格雷 75mg/天和阿司匹林 75mg/天。
- ✧ 从第 22±2 天随访到第 90±7 天（疗程不超过 75 天）：氯吡格雷 75mg/天和阿司匹林安慰剂 75mg/天。

*在第 1 天给予阿司匹林的总剂量(75mg-300mg)包括在第 1 天内任何时间、任何地点（包括在急诊室）给予患者的阿司匹林。

第二组:

- ✧ 第 1 天*：氯吡格雷安慰剂 300 mg 和公开标签的阿司匹林 75mg-300mg。
- ✧ 从第 2 天到第 21±2 天：氯吡格雷安慰剂 75mg/天和阿司匹林 75mg/天。
- ✧ 从第 22±2 天随访到第 90±7 天（疗程不超过 75 天）：氯吡格雷安慰剂 75mg/天和阿司匹林 75mg/天。

*在第 1 天给予阿司匹林的总剂量(75mg-300mg)包括在第 1 天内任何时间、任何地点（包括在急诊室）给予患者的阿司匹林。

研究药物应在随机化后 1 小时内尽快开始使用。

7 研究药物处理

7.1 药物提供与储存

赛诺菲-安万特公司提供该项双盲研究使用的药物（研究药物与安慰剂）。研究药物将被贮存在安全的地方，由研究者或其他授权人员直接负责管理，并按照标签所描述的条件进行储存。

7.2 包装和标签

每个患者的药盒均要根据患者的随机号进行标注

根据研究和访视周期的设计，研究药物包装为公用药盒和患者药盒两个药盒。其中患者药盒内含两个小药盒，每个小药盒中又分为两部分（两袋）。具体如下：

公用药盒：内含公开标签的阿司匹林（用“A_0”表示）。

包装分为两种规格：第一种规格为 50mg/片，12 片/板，共 15 板，以及 25mg/片，30 片/板，共 1 板，用于第 1 天。一个公共药盒中的阿司匹林可供 30 个患者使用。

患者药盒：包括小药盒 1 和小药盒 2。

小药盒 1 有 2 个药袋：一袋是非公开标签的氯吡格雷或氯吡格雷安慰剂：75mg/片，7 片/板，4 板，用于第 1 天到第 21±2 天。另一袋是非公开标签的阿斯匹林：25mg/片，30 片/板，2 板+6 片，用于第 2 天到第 21±2 天。

小药盒 2 有 2 个药袋：一袋是非公开标签的氯吡格雷或氯吡格雷安慰剂：75mg/片，7 片/板，11 板。另一袋是非公开标签的阿斯匹林或阿斯匹林安慰剂：25mg/片，30 片/板，8 板。均用于第 21±2 天到 90±7 天。

标签的内容将符合当地的管理规范与要求

7.3 职责

研究者、医院的药剂师或其他储存和分发药物的人员应确保在临床实验中使用的研究药物按照申办方的要求进行

安全保管和使用，并遵循现有规章制度。

所有的研究药物将根据研究者的处方进行分发，研究者有责任保证正确记录研究药物的分发和回收。

在研究药物接收和使用中出现的任何质量问题(如：研究药物在外观、标签、有效天期等方面的缺损)应该及时向申办方汇报。

在任何情况下研究者均不能向第三方提供研究药物。除按临床试验方案要求进行使用外，研究药物不能通过任何方式使用和处理。

7.4 伴随治疗

7.4.1 禁忌的伴随用药

在研究过程中使用以下药物是违背方案的。但是如果临床需要，则主治医生将需要慎重考虑使用这些干预措施。

- ✧ 标签公开的阿司匹林(除第 1 天外)；
- ✧ 非甾体抗炎药，Cox1 和 Cox2 抑制剂。如果绝对需要，非甾体抗炎药服用时间应小于 5 天，并且开始使用时间不早于随机化分组的第 8 天；
- ✧ 标签公开的噻吩吡啶(噻氯吡啶，氯吡格雷)；
- ✧ 双嘧达莫；
- ✧ 所有肝素类药物；
- ✧ 口服抗凝药物；
- ✧ IIb/IIIa受体拮抗剂；
- ✧ 溶栓药物；
- ✧ 血管干预措施（血管外科手术和/或任何血管成形术）。

如果在随机化后的 3 个月内绝对需要此类干预措施，研究药物应在干预实施 5 天前停止使用。除非患者需要服用

公开标签的氯吡格雷或阿司匹林，研究治疗将立即重新启动。在这种情况下，只有当公开标签的抗血小板治疗结束后，研究药物才可以被重新启动。

7.4.2 允许的伴随用药

除以上列出的药物单之外的任何用药(包括抗高血压药物)都是允许的。若对患者有必要，研究者慎重考虑后应尽可能给予患者稳定的剂量。由于不确定泵抑制剂（如奥美拉唑等）与氯吡格雷药物之间存在相互影响，因此既往服用质子泵抑制剂的患者应使用其他药物进行替换（如 H2 受体抑制剂），需要治疗的患者应优先使用 H2 受体抑制剂等药物而尽量避免使用质子泵抑制剂。同样，与氯吡格雷有相互作用的药物都应该尽量避免使用，这些药物包括：艾美拉唑（耐信）、西咪替丁（包括处方和非处方药物）、氟康唑（大扶康）、酮康唑（里素劳片）、伏立康唑（威凡）、依曲韦林、非尔氨酯、氟西汀（百优解，奥氮平氟西汀）、氟伏沙明（兰释）

研究期间，任何在随机化前进行的治疗和/或开立的处方或研究过程中的任何用药改变都应记录在病例报告表中。

7.4.3治疗依从性和可靠性

✧ 患者的依从性通过每次随访时计算回收药片的数量来进行评估。

✧ 研究者（或代表）应完成病例报告表中的相应页和研究药物记录表格。

✧ 必须记录研究药物中断的天期。

7.5 患者暂时停药、永久停药或失访的处理方案

✧ 研究药物应尽可能持续使用。如果停用研究药物，应该判断是否能暂时停药；永久停药是最后的方式。任何停药均应完整记录在 CRF 的相应页面上。在任何情况下，患者应尽可能长的参加试验。

✧ 在任何情况下，妊娠都将导致永久性停止试验。

7.5.1暂时停止应用研究药物

一旦研究者根据其最佳临床或实验室监测判断(见附表 5)认为研究药物不太可能与发生的事件相关，且在没有其他继续研究禁忌的情况下，应重新服用药物。重新服用药物应该在严密合理的监测下进行。

如果确定可以重新开始试验，研究人员应将所有暂时性试验中止（小于10天）重新开始的时间记录在CRF的相应页面上。

7.5.2 明确停止应用研究药物的指征

在下列情况下患者应停止应用研究药物：

- ✓ 要求停药的临床并发情况（例如化验值异常，见附件5）
- ✓ 妊娠试验阳性或有妊娠的愿望
- ✓ 避孕终止

7.5.3 对永久停止用药患者的处理方案

- ✓ 对患者的随访应遵照研究方案特殊说明的程序，持续到研究方案预定的研究结束时间，或患者从不良事件中恢复到正常或病情稳定的时间（二者取较长的时间）。
- ✓ 研究者应将所有确定的中途退组记录在CRF的相应页面上。
- ✓ 所有在最后一次随访前停止使用研究药物的患者应该在3个月时完成终点随访。
- ✓ 对于失访的患者，其CRF均应记录到最后一次随访。研究者应尽最大努力与每个患者联系，确定患者失访的原因并判断其健康状况。

7.5.4 结局

- ✓ 已经从研究中撤出的患者不能再进入研究。该患者的随机码和治疗药物将不能继续使用。

✓ 研究者应与申办方联系共同确认中断治疗和/或患者的撤出。

✓ 已随机化的患者将不会被取代。

7.5.5 研究药品的回收和销毁

✓ 研究者（或药剂师）应建立回收研究药物的详细记录，研究者和监查团队应共同确认该记录。

✓ 研究者不能破坏未使用或已被部分使用的研究药品，除非申办方提供书面授权。

若研究药物在质量方面存在缺陷，申办方将采取回收程序进行回收。在这种情况下，为召回研究药物和消除潜在危害，研究者有责任满足申办方提出的任何要求。

7.6 盲法系统和紧急揭盲程序

7.6.1 盲态方式描述

本随机、双盲研究的主要目的是比较氯吡格雷与阿司匹林联合应用，之后单独应用氯吡格雷组与单独使用阿司匹林组疗效的差异。

研究使用的两种氯吡格雷片剂(75mg有效的氯吡格雷和氯吡格雷安慰剂)是难以辨别的(其大小、形状、颜色、外观完全相同)。

研究使用的两种阿司匹林片剂(75mg 有效的阿司匹林和阿司匹林安慰剂)是难以辨别的(大小、形状、颜色、外观完全相同)。

在本研究中，分中心使用的生物学实验没有揭盲的可能。

研究者不能揭盲随机码（治疗码），除非出现特殊情况。例如，发生严重不良事件（SAE）时，公开研究药物信息对治疗受试者非常重要的情况下，才可以揭盲研究药物。

7.6.2 患者随机分组的方法

随机码列表将在合同研究组织（CRO）集中生成。

患者的药物将按照随机码表进行包装。在治疗期间，患者将接受氯吡格雷/阿司匹林组或者阿司匹林组的研究药物治疗，分配到两组的随机概率为1:1。

将根据随机化时发病时间是否超过12小时进行分层随机分组。

在第一天(基线随访)时随机顺序表将由计算机系统自动生成，受试者将按照入组的先后顺序，由小到大依次获得指定的随机试验药物编号，之后研究者将给患者与号码相应的药物。根据各中心的研究进展，可调配入选的病例数，但需要得到数据管理中心的确认。

7.6.3 研究过程中的紧急破盲

如果出现不良事件（AE），在特殊的情况下，即当了解药物成分对患者的治疗十分必要时，才能够进行破盲。如果可能，研究者在破盲前应该与监查团队联系。

如果研究分中心的研究者认为有必要破盲，他/她必须立即通知该分中心负责人，并在分中心负责人同意后尽快通知监察员和申办方。所有的电话将由CRO记录。

如果破盲，研究者应书面记录破盲天期、时间和原因，研究药物将停止使用。

8 患者安全

8.1 不良事件监测

所有不良事件将遵循相应法规进行处理和报告，其报告将包括在最终的临床试验报告中。

8.2 不良事件(AE)和严重不良事件(SAE)定义

不良事件是指受试者因服用研究药物或在研究中发生的任何医源性不利事件，无论是否与服用研究药物或治疗过

程有因果关系。

除了因为事件的过程、严重性或其他特征，研究者根据他的最佳临床判断，认为在这种临床情况下该事件应被考虑为例外事件时，终点事件不被考虑为不良事件。

严重不良事件是服用任何剂量药物出现的不良事件

- 死亡
- 威胁生命的

备注：危及生命，其严重程度的定义是指事件发生当时将危及患者生命，而并非假设事件如果更严重时将导致患者死亡。

- 需要住院治疗或是延长住院时间
- 导致永久性或严重残障
- 先天性的缺陷或出生缺陷
- 重大医源性事件

在其它情况下，应运用医学和科学的决策来判断迅速上报是否合适。例如某事件可能并不威胁生命、导致死亡或需要住院治疗，但是有可能对患者造成危害，或是需要干预以预防定义中描述的不良后果，则该事件被认为是严重不良事件，需要迅速上报。

这些通常被认为是严重的事件。

备注：例如：在急诊室/家中的对过敏性支气管痉挛的强化治疗、血液病、惊厥或无症状的ALT升高≥10单位，虽然并不导致住院，药物依赖或滥用，也应被视为严重不良事件。

8.3 研究者在安全性报告方面的职责

8.3.1 不良事件

任何不良事件，不论其严重程度如何，是否与研究药物相关，从临床研究方案第一天访视或签署知情同意书（例如出现在洗脱期）后开始，到研究方案计划的最后一次随访结束为止，都应记录在病例报告表里的相应页面。在任何可能的情况下，患者出现的症状都应被分组为某个单独的综合征或临床诊断。研究者应具体描述事件发生的时间、事件强度、对研究药物采取的相应措施、给予的对症治疗、结局以及他/她关于该不良事件是否有可能由研究药物导致的判断。

如果化验检查，生命体征或心电图异常与研究药物之间具有医学相关性：例如出现临床症状、需要对症治疗、导致停药和/或严重后果，它们将被作为不良事件记录。

8.3.2 严重不良事件

对于严重不良事件，研究者必须立即采取行动：

立即通知申办方的相应负责人，发送有签字和天期的病例报告表中的相应页给申办方的相应负责人，附加所有检查的复印件和这些检查完成的天期。应确保患者隐私得到保护，确保在提供给申办方的临床原始资料的复印件中去除患者的身份信息。实验室结果应包括正常范围值。

对任何严重不良事件的随访应该在该事件发生后一周内完成。并将严重不良事件填写在 CRF 相应位置，签字后最好以传真的方式报告给监测中心，监测中心的名称，地址，传真号将在临床试验方案中注明。

8.3.3 随访

研究者应采取所有合理的措施来确保患者的安全。研究者应该追踪任何有关不良事件的结果（临床症状、体征、实验室检查结果等），直到患者恢复正常或病情稳定。

如果出现任何严重不良事件，研究者应追踪患者，直到临床症状完全缓解且实验结果恢复正常或直到病情稳定后。这意味着在患者退出临床试验后随访仍将继续。监查团队有可能要求额外的研究。

在研究药物终止后，研究者应注意任何时间出现的任何严重不良事件。

9 研究流程

9.1 第一天访视=筛选+入组+基线访视

9.1.1 筛选和入组

将核实入选，排除标准，并且：

对筛选对象进行 $ABCD^2$ 评分（针对 TIA 患者）和神经系统评估(mRS 和 NIHSS 评分)。

对筛选对象进行 12 导联心电图检查以排除房颤。进行头 CT 或 MRI 检查以排除出血、血管畸形、肿瘤或脓肿。由于心电图和脑影像学检查被常规推荐用于所有 TIA 和小卒中患者，本研究将不提供这些费用。

研究者应完成包括所有筛选对象在内的一份筛选表。这些筛选表用来决定不同患者群是否具有代表性及确认分中心的参与。

患者将收到完整的研究相关信息，包括口头及书面的。

符合入组标准而不符合排除标准的患者将被邀请参加本研究。在入组之前患者应签署知情同意书。

9.1.2 基线期评估

基线期评估包括：患者的人口学信息、本次脑血管事件的症状、服药史、既往史、家族史、吸烟饮酒史、体检结果、治疗前mRS。

将对筛选对象进行实验室检查：血肌酐、血糖、中性粒细胞计数、白细胞计数、血小板计数、凝血象等。

将对筛选对象进行查体：体重、生命体征（卧位收缩压/舒张压/心率）。

将使用标准化仪器记录筛选对象的脑影像学检查、心电图检查结果。

9.1.3 随机化

统计学家将制定一份专业的随机表，确保治疗药物在每一个参与中心平均分布。如果患者同意参与试验，研究者将根据患者入组的先后顺序取得对应随机号，该随机号将记录在入组筛选表及 CRF 表上。

9.1.4 第 1 天的治疗

患者将收到第1天的研究药物，将被指导如何服用研究药物。研究药物首次服用的时间将被记录。

研究药物应在随机分组后尽快使用（在随机化后1小时之内）。

研究者将酌情给予阿司匹林剂量（第一天总剂量在 75-300mg 之间）。

将收集每位患者的以下信息：

- ✧ 人口学信息（年龄、性别、种族）；
- ✧ 患者服药史及伴随疾病；
- ✧ 合并用药
- ✧ 下次访视时间（随机化第21± 2天）

9.2 21 天随访=第 21±2 天

这次访视期间：

- ✓ 进行神经系统检查（mRS和NIHSS评分）；
- ✓ 进行查体：体重、生命体征（卧位收缩压、舒张压、心率）；

- ✓ 应收集自上次随访以来合并用药及不良事件的信息；
- ✓ 收集整个研究过程中（第1天，第2天到第21±2天）第1个盒子中未服用的药物，用以判断用药量及评价患者的依从性；
- ✓ 研究者将从第2个药盒中发放给患者第22±2天到第90±7天的药物，并且指导患者从本次随访到下次随访期间如何服药
- ✓ 与患者预约下一次随访时间（随机化后90±7天）

9.33 个月随访=第 90±7 天

注意：第 21 天和第 3 个月之间随访的天数不应超过 75 天

本次随访期间：

- ✓ 如果患者被诊断为症状性颅内大动脉狭窄（sICAD），应强烈建议完成其MRI+MRA序列(MRI序列包括T1+T2+DWI+FLAIR+T2*)检查。所有图像应用DICOM格式保存，DICOM光盘将被传递到中心影像评价实验室；
- ✓ 进行神经系统检查（mRS和NIHSS评分）；
- ✓ 生存质量评价（EQ-5D量表）(见附表4)；
- ✓ 进行查体：包括生命体征（左侧收缩压、舒张压、心率）；
- ✓ 应收集自上次随访以来合并用药及不良事件的信息；
- ✓ 收集整个研究过程中治疗盒中未使用的药物，用来计算用药量及评价患者的依从性。

9.4 主要有效性终点事件访视

如果患者发生可疑的神经系统临床症状，包括原缺血脑血管病恶化，出现新的短暂的或持续的神经系统症状。分

中心将在事件发生72小时内提交事件判读资料。包括以下内容：

- ✓ 进行神经系统检查（mRS和NIHSS评分）；
- ✓ 进行查体：包括生命体征（左侧收缩压、舒张压、心率）；
- ✓ 如果患者被诊断为症状性颅内大动脉狭窄（sICAD），应强烈建议完成其MRI序列(MRI序列包括T1+T2+DWI+FLAIR+T2*)检查。所有图像应用DICOM格式保存，DICOM光盘将被传递到中心影像评价实验室；
- ✓ 如果患者发生新的可疑心脏病事件，要进行心脏评估（包括心电图检查）。如果有支持心肌梗死的临床信息需要及时收集并在72小时内上报给CRO以进一步判读；
- ✓ 应收集自上次随访以来合并用药及不良事件的信息。

10 统计学方案

10.1 统计分析方案

这部分是统计学分析的概述。完整的详细描述请见统计分析计划书（SAP）。它对如何收集数据和在临床研究报告中陈列数据进行了总体规定。最终版的 SAP 将会数据库锁定和揭盲前出版。SAP 将规定所有“预先规定的、计划进行的分析”。

10.1.1 样本量估算

10.1.1.1 主要无效假设

在 TIA 和小卒中患者症状出现 24 小时内使用 3 个月氯吡格雷（起始剂量 300mg）合并前 21 天使用阿司匹林（75mg/天）与单独使用阿司匹林（75mg/天）90 天随访时发生主要终点事件(缺血性卒中和出血性卒中)的风险无差异。

本试验的最小样本量由试验预期的最小需求决定，也就是试验组与安慰剂组的出现具有临床意义的差异所需要的最小样本量。相对危险度降低 22%(氯吡格雷相对危险度是 0.78)是我们期望达到的最低程度的差异标准。

预计如果样本量达 5100 人，在双侧检验 α =0.05 的条件下，我们有 90%的把握可观测到相对危险度降低 22%，但有 5%脱落率（药物依从性差）(图 2 和表 2)。样本量公式基于通常的两组对比人数量求得。公式会给我们需要做的生存分析保守的样本量估计值。

表 2. 对于对照组结果的不同风险(12%到 17%)来计算样本量大小

机率	n 脱落	5%脱落	治疗组 结局风险	对照组 结局风险	氯吡格雷的 相对危险度
0.8	2880	3024	13%	17%	0.78
0.8	3094	3249	12%	16%	0.78
0.8	3334	3501	12%	15%	0.78
0.8	**3608**	**3788**	**11%**	**14%**	**0.78**
0.8	3926	4122	10%	13%	0.78
0.8	4296	4511	9%	12%	0.78
0.9	3856	4049	13%	17%	0.78
0.9	4140	4347	12%	16%	0.78
0.9	4462	4685	12%	15%	0.78
0.9	**4830**	**5072**	**11%**	**14%**	**0.78**
0.9	5254	5517	10%	13%	0.78
0.9	5750	6038	9%	12%	0.78

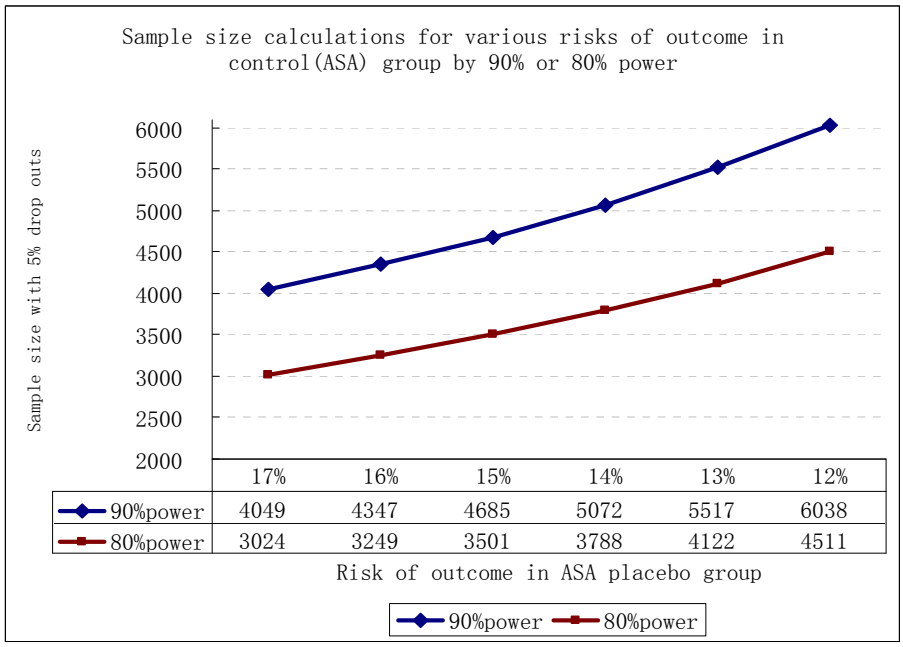


图 2. 对于对照组结果的不同风险(90%或 80%概率)来计算样本量大小

10.1.1.1.1 安慰剂组（单用阿司匹林组）终点事件的风险

根据北加州和牛津的队列研究[62]和 FASTER 预试验[56]的数据，在 TIA 高危患者(ABCD^{2}评分>4)或小卒中患者症状出现 24 小时内给予阿司匹林治疗，90 天卒中复发风险约为 14%。

表 3. 安慰剂组(ASA)结果的风险估计

人群	例数	3 个月风险	
		卒中	卒中 / 心肌梗死 / 死亡

所有 TIA[1]	2776	10.30%	12.14%
除去极小可能的 TIA[1]	2325	11.87%	14.02%
TIA 患者的 ABCD[2] 评分 [1]			
> 3	2067	12.58%	14.42%
> 4	1379	14.72%	16.75%
> 5	737	17.50%	19.94%
TIA and minor stroke [2]	194	10.8%	11.9%

[1] 基于北部加州和牛津夏州的 cohort 研究数据库[61]

[2] FASTER 试验[56]

10.1.1.1.2 氯吡格雷与阿司匹林联用的相对危险度

我们预期氯吡格雷在未联合应用阿司匹林的情况下可以降低复合终点事件（卒中、心肌梗死和心血管死亡）的风险。在 FASTER 试点试验中氯吡格雷组对比安慰剂组相对危险度降低达 34.3%（对于所有卒中），但是由于样本量过小，置信区间太宽，该数据无统计学意义。

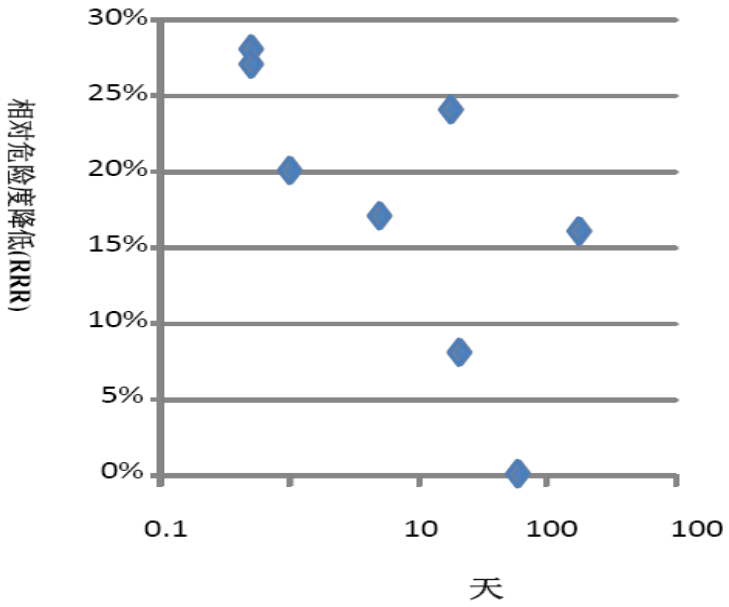
在入组标准更宽的亚组试验分析中，我们可以得到更多的 RRR 估计值，并且在长期的治疗中，药物的残留风险也可以变得更低。

在 CHARISMA 试验中，卒中/TIA 患者在卒中/TIA 发生后 21 天内联合应用氯吡格雷/阿司匹林比单独应用阿司匹林的相对危险度降低 24%。在 MATCH 试验中，卒中/TIA 患者在 MATCH 试验中，卒中/TIA 患者在卒中/TIA 发生后 7 天内联合应用氯吡格雷/阿司匹林对比单独应用氯吡格雷的相对危险度降低达 17%。基于之前的安全性结果，我们不认为 TIA

患者使用氯吡格雷将导致大量颅内出血或危及生命的出血。因此，上述实验的综合结果是使用氯吡格雷带来的明显收益并不被增加的颅内出血风险所抵消。根据这些之前的研究，我们推测相对危险度降低将大于 22%。(图 3)

图 3. 临床事件不同时间窗联合应用氯吡格雷/阿司匹林对比单独应用氯吡格雷/阿司匹林

(终点事件：卒中、心肌梗死、血管性死亡)



Trial	Days	RRR
CHARISMA	18	24%
CHARISMA	180	16%
MATCH	5	17%
MATCH	21	8%
MATCH	60	0%
FASTER	0.5	28%
CURE	1	20%
CREDO	0.5	27%

10.1.1.1.3 相对危险度的临床意义

样本量的大小取决于检测到相对危险度降低 22%的需求。基于该数据，32 名 TIA/小卒中的患者(不考虑其他危险因素)中经治疗后预期 3 个月时卒中复发事件将减少。这种效果在临床上被治疗医生所重视，在二级预防中，联用氯吡格雷/阿司匹林比单独应用阿司匹林能给患者带来更大收益。

10.1.1.1.4 症状发生与入组之间的间隔 t

由于入组延误，卒中很可能在患者随机化入组前发生。在 TIA 症状发作 24 小时内发生重大事件的患者应该从事件发生率的分析中剔除，因为许多这样的患者在终点事件发生之前还没有入组和接受治疗。

10.1.1.1.5 失访

这些计算结果允许 5%的中途脱落率（药物非依从性）。

10.1.1.1.6 把握度与α值

一个不确定的假设用来推测有效性及事件发生率，我们选择一个样本量来提供 90%的把握或机率（双侧检验，α等于 5%）。总之，每组大约 2550 患者(样本总数 5100)有 90%的概率检测到相对危险度降低 22%，双侧检验α等于 0.05，并且 5%脱落信息（药物非依从性）（表 2，图 2）。（增加氯吡格雷后相对危险度（RR）是 0.78）。

10.2 统计分析

详细的统计分析计划将在试验启动期制定，包括所有分析的表格和细节。

10.2.1 主要终点事件

主要分析采用意向性治疗分析方法，包括接受首次研究药物的受试者。缺失值将仍然按缺失对待，患者在最后一次随访时将接受检查（临床事件的时间，研究结束时，或在失访前的最后一次随访时）。我们将用 Kaplan-Meier 曲线模拟 90 天随访时的卒中（缺血性或出血性）的累积风险，使用 Cox 比例风险模型计算风险比例和 95％可信区间，使用 Log-rank 检验评估疗效。所有统计数据都将采用双侧检验，P<0.05 被认为有统计学意义

10.2.2 次要终点事件

多数次要结局分析也将采用主要结局分析策略。对于连续性变量（如成本和 MOCA），我们将使用多元线性回归分析。连续变量将检查大致正常和异方差残差和离群。转换和/或加权最小二乘法将被视为补救措施的非正常和异方差。转换和/或加权最小二乘法将被视为补救措施。极端值进行有效性检查，将对结论进行灵敏度分析。

11 伦理及调控规程

11.1 伦理原则

本临床试验遵循第 18 届世界医学宣言（赫尔辛基，1964），所有应用修正案将在第 18 届世界医学宣言和 ICH 指南

中的药品临床试验管理规范指导下展开。

11.2 法律法规

本临床试验管理将遵循国际法律法规，并遵循试验所在地中国的法律法规以及任何有关应用的指导方针。

11.3 知情同意书

研究者(根据相应法规的要求)或由研究者授权并负责的人员，应该充分告知受试者包括伦理委员会许可的书面信息在内的临床试验的所有相关问题。研究者应该用受试者可以理解的语言或术语最大程度的告知其有关研究的信息

在参与临床试验之前，患者本人或其法定代表应与患者讨论知情同意的研究人员共同签署知情同意书（姓名及天期）。研究者应向患者提供已签署的知情同意书的复印件。

在递呈给伦理委员会审核之前，研究者所使用的知情同意书应由资助方审阅并批准。

11.4 审查机构/独立的伦理委员会(IRB/IEC)

在试验开始前，研究者或申办方必须向伦理委员会递交临床试验方案，研究者须向申办方递交伦理委员会签署书面的同意意见的复印件。

临床试验（研究编号、研究方案名称、版本号），审阅过的文件（包括临床研究方案、知情同意书、研究者操作手册、研究者简历等），投票成员的资格认定及审阅天期等都应清楚地记录在伦理委员会同意书上

在试验开始之前研究药物不得向研究中心发放，在直到获得申办方收到并注明签署天期的书面同意书的复印件前临床研究不得开始。

在临床试验过程中，对所有试验方案的任何修改应向伦理委员会报告，经批准后方能执行。在试验中发生的任何可能影响患者安全或临床试验继续展开的事件，尤其是安全性的改变均应向伦理委员会报告。研究者操作手册的更新应递交给伦理委员会。

如果需要，每年应向伦理委员会递交临床试验的进展报告和临床试验结束后的临床结果摘要。

12 研究监查

12.1 研究者职责

研究者保证在进行临床试验时遵循临床试验方案，遵循 ICH 指南中的药品临床试验管理规范以及相应法律法规。

研究者应保证遵循临床试验方案中的和由申办方提供的所有研究操作（包括安全性原则）。研究者应根据相关要求，以一种准确、清晰的方式（病例报告表[CRF]、偏差解析表[DRF]及其它方式）提供可靠数据和临床试验方案要求的所有信息，并确保申办方代表可直接查看原始资料。

研究者可能会任命他/她认为合适的人作为协助研究者。协助研究者将根据临床试验方案协助进行临床试验的管理。所有的协助研究者将被及时任命并记录。协助研究者接受研究者的监督和管理。研究者将提供给他们一份临床试验方案和所有必需的信息。

临床试验的申办方对卫生当局负责，通过采取所有适当的手段来确保临床试验的合理管理，这些手段如伦理、临床试验方案依从性、记录在病例报告表中数据的完整性和有效性等。因此，监查团队的主要责任是帮助研究者和申办方保证临床试验各个方面的高度的伦理性、科学性、专业性和规范性。

监查团队将定期通过现场访视、信件或电话形式与每个中心联系，将派出代表来评估研究进展、研究者和患者对临床方案的依从性以及解决紧急的问题。在这些监查访问中，监查员将和研究者共同监查，要点如下（并非无遗漏）：患者的知情同意、患者的招募和随访、严重不良事件文件的记录和报告、研究药物发放、研究药物组患者的依从性、研究药物计数，伴随治疗和数据的质量。

12.2 原始数据要求

根据 ICH 指南中的 GCP 原则，监督团队应对照原始资料来核查 CRF。知情同意书将包括一个声明，即患者允许已授权的申办方、伦理委员会、权威机构直接查阅病例报告表上相关的原始资料(如患者的医疗档案、预约记录、原始实

验室记录等)。上述人员应遵循职业保密规定，必须对患者的所有个人身份信息或医疗信息保密。

12.3 病例报告表(CRF)的使用、完成及附加要求

研究者有责任保证恰当、正确填写 CRF，记录(根据资助方的指示)所有的观察和相关临床研究的其它数据。所有的 CRF 应该以一种整洁的、清晰的方式完整的完成，从而确保数据被正确解释。

如果信息需要修改，不应进行涂改或覆写，正确的信息应写在原始信息旁边，并由修改人签名及注明天期。

CRF 将分为两份，一份保留在分中心，一份递交给申办方。

申办方收到 CRF 后进行计算机数据分析，可能会产生额外需求，研究者必须通过证实或修改数据的方式来回答这些需求。更正的内容将通过研究者和申办方附加到 CRF。

12.4 计算机化系统应用

电脑系统用于建立，修改，维护，存档，检索和传输数据（包括 IVRS，监测工具，数据录入和统计分析)。

13 研究结果公布

执行委员会将按照管理条例和程序来公布该试验的结果。数据库锁定后试验结果将尽快被公布。

在 5100 例 TIA 或小卒中患者研究人群中，本试验将对其治疗效果、医疗措施及临床结局进行详细地资料分析。当然，被咨询的 CHANCE 生物统计学专家是不可能识别出此试验的任何患者；这就可能要求去除或整合一些特定的统计学变量；同时，访问数据集也不需要提供数据使用协议。最后，以逗号分隔的文本格式的磁盘存储数据（包括文本格式的数据字典）将送至有合作意向的第三方机构处理。

14 辅助研究

辅助研究方案将由执行委员会审查。因为需要收集额外的研究数据，不强行要求，但是鼓励分中心参加这些辅助研究。执行委员会将按照管理条例和程序来公布该试验的结果。

15 参考文献

1. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH,Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. Lancet Neurol 2007;6(5):456-64.

2. Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. Circulation 2001;103(3):462-8.

3. Shi FL, Hart RG, Sherman DG,Tegeler CH. Stroke in the People's Republic of China. Stroke 1989;20(11):1581-5.

4. Brown RD Jr, Petty GW, O'Fallon WM, WiebersDO,WhisnantJP.Incidence of transient ischemic attack in Rochester, Minnesota, 1985-1989. Stroke 1998;29(10):2109-13.

5. Wolf, P.A. and L.A. Cupples. Incidence and prevalence of transient ischemic attack. In: W.S. Moore, ed. Surgery for Cerebrovascular Disease. New York:Churchill Livingstone,1987.

6. Edlow JA, Kim S, Pelletier AJ,Camargo CA Jr. National study on emergency department visits for transient ischemic attack, 1992-2001. AcadEmerg Med 2006;13(6):666-72.

7. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998;29(2):415-21.

8. Yi Long Wang, Di Wu, Xiaoling Liao, Wei Zhang, Xingquan Zhao, Yong Jun Wang.Burden of

stroke in China. International Journal of Stroke 2007;2(3):211-213.

9. Wang W, Zhao D, Wu G, Liu J, Liu S, Qin L, et al. Trend analyses in the incidence of acute intracerebral hemorrhage events and acute cerebral infarction events in urban areas in Beijing. Zhonghua Liu Xing Bing XueZaZhi 2002;23(5):352-5.

10. Jiang B, Wang WZ, Chen H, Hong Z, Yang QD, Wu SP, et al. Incidence and trends of stroke and its subtypes in China: results from three large cities. Stroke 2006;37(1):63-8.

11. Zhao D, Liu J, Wang W, Zeng Z, Cheng J, Liu J, et al. Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project. Stroke 2008;39(6):1668-74.

12. Rothwell PM, Buchan A,Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. Lancet Neurol 2006;5(4):323-31.

13. Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Jimenez-Conde J, Pont-Sunyer C, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke 2008;39(6):1717-21.

14. Johnston SC, Gress DR, Browner WS,Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284(22):2901-6.

15. Coull AJ, Lovett JK,Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328(7435):326.

16. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and

short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36(4):720-3.

17. Gladstone DJ, Kapral MK, Fang J, LaupacisA,Tu JV. Management and outcomes of transient ischemic attacks in Ontario. CMAJ 2004;170(7):1099-104.

18. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, SvensonLW,Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62(11):2015-20.

19. Eliasziw M, Kennedy J, Hill MD, Buchan AM,Barnett HJ. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ 2004;170(7):1105-9.

20. Friedman GD, Wilson WS, Mosier JM, ColandreaMA,Nichaman MZ. Transient ischemic attacks in a community. JAMA 1969;210(8):1428-34.

21. Ueda K, Kiyohara Y, Hasuo Y, Yanai T, Kawano H, Wada J, et al. Transient cerebral ischemic attacks in a Japanese community, Hisayama, Japan. Stroke 1987;18(5):844-8.

22. Whisnant JP, Matsumoto N,Elveback LR. Transient cerebral ischemic attacks in a community. Rochester, Minnesota, 1955 through 1969. Mayo ClinProc 1973;48(3):194-8.

23. Dennis MS, Bamford JM, SandercockPA,Warlow CP. A comparison of risk factors and prognosis for transient ischemic attacks and minor ischemic strokes.TheOxfordshire Community Stroke Project. Stroke 1989;20(11):1494-9.

24. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med

1995;333(24):1581-7.

25. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. Neurology 2005;64(4):654-9.

26. Weinberger J. Antiplatelet agents for stroke prevention following transient ischemic attack. South Med J 2008;101(1):70-8.

27. Emre U, RantanenK,Tatlisumak T. Antithrombotic treatment in the prevention of ischemic stroke. Curr Drug Targets 2007;8(7):817-23.

28. Albers GW. Antithrombotic therapy for prevention and treatment of ischemic stroke. J Thromb Thrombolysis 2001;12(1):19-22.

29. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349(9066):1641-9.

30. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349(9065):1569-81.

31. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31(6):1240-9.

32. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the

early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38(5):1655-711.

33. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA, et al. National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol 2006;60(3):301-13.

34. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39(5):1647-52.

35. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37(2):577-617.

36. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25(5):457-507.

37. Halkes PH, van Gijn J, Kappelle LJ, KoudstaalPJ,Algra A. Aspirin plus dipyridamole versus

aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006;367(9523):1665-73.

38. Diener HC, Cunha L, Forbes C, Sivenius J, SmetsP,Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J NeurolSci 1996;143(1-2):1-13.

39. Diener HC, Sacco R,Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartanversus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). Cerebrovasc Dis 2007;23(5-6):368-80.

40. Ralph L. Sacco, on behalf of the PRoFESS Study Group. Prevention Regimen For Effectively avoiding Second Strokes - The PRoFESS Trial Results. Presented at European Stroke Conference 2008.

41. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. Drugs 2007;67(4):613-46.

42. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. Drugs 2000;60(2):347-77.

43. Sharis PJ, Cannon CP,Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. Ann Intern Med 1998;129(5):394-405.

44. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348(9038):1329-39.

45. Helft G, Osende JI, Worthley SG, Zaman AG, Rodriguez OJ, Lev EI, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. ArteriosclerThrombVascBiol 2000;20(10):2316-21.

46. Savcic M, Hauert J, Bachmann F, Wyld PJ, GeudelinB,Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. SeminThrombHemost 1999;25Suppl 2:15-9.

47. Herbert JM, Dol F, Bernat A, Falotico R, LaleA,Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. ThrombHaemost 1998;80(3):512-8.

48. Harker LA, Marzec UM, Kelly AB, Chronos NR, Sundell IB, Hanson SR, et al. Clopidogrel inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. Circulation 1998;98(22):2461-9.

49. Makkar RR, Eigler NL, Kaul S, Frimerman A, Nakamura M, Shah PK, et al. Effects of clopidogrel, aspirin and combined therapy in a porcine ex vivo model of high-shear induced stent thrombosis. Eur Heart J 1998;19(10):1538-46.

50. Jauhar R, Bergman G, Savino S, Deutsch E, Shaknovich A, Parikh M, et al. Effectiveness of aspirin and clopidogrel combination therapy in coronary stenting. Am J Cardiol 1999;84(6):726-8, A8.

51. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99(18):2364-6.

52. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, TognoniG,Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(7):494-502.

53. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288(19):2411-20.

54. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364(9431):331-7.

55. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354(16):1706-17.

56. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, DemchukAM,Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol 2007;6(11):961-9.

57. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111(17):2233-40.

58. Hart RG, Easton JD. Do we really need a better way to give heparin in acute cerebral

ischemia?. Stroke 2002;33(3):659-60.

59. Adams HP Jr, Woolson RF, Clarke WR, Davis PH, Bendixen BH, Love BB, et al. Design of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Control Clin Trials 1997;18(4):358-77.

60. Johnston SC. Towards FASTER treatment of TIA and minor stroke. Lancet Neurol 2007;6(11):941-3.

61. Salthouse TA. The role of memory in the age decline in digit-symbol substitution performance. J Gerontol 1978;33(2):232-8.

62. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369(9558):283-92.

16 附件：

附表 1. 终点事件定义

卒中	突然发生的局灶性神经系统症状及体征，与脑循环障碍相关。将根据 SSS-TOAST 标准进行病因分型。
缺血性卒中	急性局灶性脑或视网膜梗死。标准：（1）急性发作的新的局灶性神经功能缺损的临床征象或影像学证据持续时间超过 24 小时，排除其他非缺血性病因（如脑部感染，脑外伤，脑肿瘤，癫痫，严重的代谢性疾病或退行性神经系统疾病）；或(2) 急性脑或

	视网膜缺血事件，排除其它非缺血性病因，局灶症状或体征持续时间小于 24 小时，但伴有影像学上新发梗死灶证据；或(3)原有血管源缺血性卒中进展（即在原发缺血性卒中基础上 NIHSS 增加≥4，不包括梗塞后出血转化或症状性颅内出血）持续时间大于 24 小时，伴有头 MRI 或 CT 上的新的缺血性改变。
出血性卒中	突发的血液渗出至脑实质或蛛网膜下腔引起的神经系统症状。脑梗死出血转换将归为脑梗死其中一类。
TIA	急性发作的局灶性脑或视网膜缺血，持续时间小于 24 小时，影像学上不存在脑梗死证据。排除其他非缺血性病因（如脑部感染，脑外伤，脑肿瘤，癫痫，严重的代谢性疾病或退行性神经系统疾病）。
症状性脑出血	血液破入至脑实质并伴有临床神经功能恶化，恶化的定义为 NIHSS 增加大于等于 4 分，或者由神经功能恶化导致的死亡。脑出血定义为急性的血液破入脑实质。脑出血诊断标准：影像学检查、手术或尸检证实存在脑实质内血肿。
非症状性脑出血	血液破入至脑实质不伴有临床神经功能恶化。脑出血诊断标准：影像学检查、手术或尸检证实存在脑实质内血肿。
其他症状性颅内出血	血液破入颅内并伴有神经功能恶化。神经功能恶化定义为 NIHSS 增加大于等于 4 分，或者由神经功能恶化导致的死亡。颅内

	出血定义为血液破入蛛网膜下腔、硬膜外或硬膜下并伴有临床症状，其断标准：影像学检查、手术或尸检证实存在蛛网膜下腔、硬膜外或硬膜下血肿。
其他非症状性颅内出血	血液破入颅内不伴有神经功能恶化。颅内出血诊断标准：影像学检查、手术或尸检证实存在蛛网膜下腔、硬膜外或硬膜下血肿。
心肌梗死后冠状动脉再通治	存在心急梗死的证据，并给与冠状动脉再通治疗。心肌梗死诊断采用国际通用标准(Circulation 2007 116:2634-2653），参考心脏标记物、心电图（ECG)、临床表现、影像检查和病理检查 5 项诊断指标。
心肌梗死后无冠状动脉再通治	存在心急梗死的证据，未给与冠状动脉再通治疗。心肌梗死诊断采用国际通用标准(Circulation 2007 116:2634-2653），参考心脏标记物、心电图（ECG)、临床表现、影像检查和病理检查 5 项诊断指标。
冠状动脉再通治非心肌梗死性冠状动疾病	治疗非心肌梗死的冠状动脉疾病而进行的增加冠状动脉血流量的手术。包括：冠状动脉造影、支架植入术或冠状动脉搭桥术。
缺血性血管源性死亡	由缺血性卒中、心肌梗死、心律失常、肺动脉栓塞、肠或肢体梗死导致的死亡；突发心源性死亡或不能排除由非缺血性原因导致的死亡。

出血性血管源性死亡	由颅内或系统性出血导致的死亡。

附表 2. 改良 Rankin 量表的评定方法

改良 Rankin 量表是用来衡量患者脑卒中后的功能恢复的结果。黑体字显示了每一级别的正式定义。斜体字则给予了进一步指导，以期减少不同观察者间可能产生的误差，但对面谈的架构没有要求。请注意仅考虑自脑卒中以后发生的症状。假如患者无须外界帮助，可在某些辅助装置的帮助下行走，则被视为能够独立行走。

如果两个级别对患者似乎同样适用，并且进一步提问亦不太可能做出绝对正确的选择，则应选择较为严重的一级。

0-完全没有症状

尽管可能会有轻微症状，但患者自脑卒中后，没有察觉到任何新发生的功能受限和症状。

1-尽管有症状，但未见明显残障；能完成所有经常从事的职责和活动

患者有由脑卒中引起的某些症状，无论是身体上或是认知上的（比如影响到讲话、读书、写字；或身体运动；或感觉；或视觉；或吞咽；或情感），但可继续从事所有脑卒中以前从事的工作、社会和休闲活动。用于区分级别 1 和 2（见下）的关键问题可以是，“是否有些事情你过去经常做，但直到脑卒中以后你不能再做？”。频率超过每月一次的活动被认为是“经常”。

2-轻度残障；不能完成所有以前能从事的活动，但能处理个人事务而不需帮助

某些脑卒中以前可以完成的活动（如开车、跳舞、读书或工作），脑卒中后患者不再能够从事，但仍能每天照顾自己而无须他人协助。患者能够不需要别人的帮助穿衣、行走、吃饭、去卫生间、准备简单的食物、购物、本地出行等。患者生活无需监督。设想这一级别的患者可在无人照顾的情况下单独居家一周或更长时间。

3-中度残障；需要一些协助，但行走不需要协助

在这一级别，患者可以独立的行走（可借助辅助行走的机械）能够独立穿衣、去卫生间、吃饭等，但是更复杂的任务需要在别人协助下完成。例如，需要他人代替完成购物、做饭或打扫卫生的工作，和一周不止一次看望患者以确保完成上述活动。需要协助的不仅是照顾身体，更多的是给予建议：比如，在这一级别的患者将需要监督或鼓励来处理财务。

4-重度残障；离开他人协助不能行走，以及不能照顾自己的身体需要

患者需要其他人帮助打理天常生活，无论是行走、穿衣、去卫生间或吃饭。患者需要每天照看至少一次、通常是二次或更多次，或必须和看护者住得很近。为区分级别 4 和 5（见下），考虑患者是否能够在一天当中，常规单独生活适当的时间。

5-严重残障；卧床不起、大小便失禁、须持续护理和照顾

虽然不需受过培训的护士，但需要有人整个白天和夜间数次照看。

附表 3. NIHSS 评分

注意每次 NIHSS 评分时要记录实际评定的时间按表评分，记录结果。不要更改记分，记分所反映的是病人实际情况，而不是医生认为病人应该是什么情况。快速检查同时记录结果。除非必要的指点，不要训练病人（如反复要求病人做某种努力）。

如部分项目未评定，应在表格中详细说明。.

	检查	评分	分值
1a	意识水平: 即使不能全面评价（如气管插管、语言障碍、气管创伤、	0＝ 清醒，反应敏锐 1＝ 嗜睡，最小刺激能唤醒 病人完成指令、回答问	_____

	检查	评分	分值
	绷带包扎等），检查者也必须选择 1 个反应。只在病人对有害刺激无反应时（不是反射），方记录 3 分。	题或有反应 2= 昏睡或反应迟钝，需要强烈反复刺激或疼痛刺激才能有非固定模式的反应 3= 仅有反射活动或自发反应，或完全没反应、软瘫、无反应	
1b	意识水平提问： （仅对最初回答评分，检查者不要提示）询问月份，年龄。回答必须正确，不能大致正常。失语和昏迷者不能理解问题记 2 分，病人因气管插管、气管创伤、严重构音障碍、语言障碍或其他任何原因不能说话者（非失语所致）记 1 分。	0= 都正确 1= 正确回答一个 2= 两个都不正确或不能说	_____
1c	意识水平指令： 要求睁眼、闭眼：非瘫痪手握拳、张手。若双手不能检查，用另一个指令（伸舌）。仅对最初的反应评分，有明确努力但未完成也给评分。若对指令无反应，用动作示意，然后记录评分。对创伤、截肢或其他生理缺陷者，应给予一个适宜的指令。	0= 都正确 1= 正确完成一个 2= 都不正确	_____
2	凝视： 只测试水平眼球运动。对自主或反射性（眼头）眼球运动记分。若眼球恻视能被自主或反射性活动纠正，记录 1 分。若为孤立性外周神经麻痹（Ⅲ、Ⅳ、Ⅴ），记 1 分。在失语病人中，凝视是可测试的。对眼球创伤、绷带包扎、盲人或有视觉或视野疾病的患者，由检查者选择一种反射性运动来测试。建立与眼球的联系，然后从一侧向另一侧运动，偶尔能发现凝视麻痹。	0= 正常 1= 部分凝视麻痹（单眼或双眼凝视异常，但无被动凝视或完全凝视麻痹） 2= 被动凝视或完全凝视麻痹（不能被眼头动作克服）	_____
3	视野： 用手指数或视威胁方法检测上、下象限视野。如果病人	0= 无视野缺失 1= 部分偏盲 2= 完全偏盲	_____

	检查	评分	分值
	能看到侧面的手指，记录正常。如果单眼盲或眼球摘除，检查另一只眼。明确的非对称盲（包括象限盲），记 1 分。病人全盲（任何原因）记 3 分，同时刺激双眼。若人濒临死亡记 1 分，结果用于回答问题 11。	3＝ 双侧偏盲（全盲，包括皮质盲）	

	检查	评分	分值
4	面瘫： 言语指令或动作示意，要求病人示齿、扬眉和闭眼。对反应差或不能理解的病人，根据有害刺激时表情的对称情况评分。有面部创伤/绷带、经口气管插管、胶布或其他物理障碍影响面部检查时，应尽可能移至可评估的状态。	0＝ 正常 1＝ 最小（鼻唇沟变平、微笑时不对称） 2＝ 部分（下面部完全或几乎完全瘫痪，中枢性瘫） 3＝ 完全（单或双侧瘫痪，上下面部缺乏运动，周围性瘫）	_____
5	上肢运动： 上肢伸展：坐位 90°，位卧 45°。要求坚持 10 秒；对失语的病人用语言或动作鼓励，不用有害刺激。评定者可以抬起病人的上肢到要求的位置，鼓励病人坚持。仅评定患侧。	0＝ 上肢于要求位置坚持 10 秒，无下落 1＝ 上肢能抬起，但不能维持 10 秒，下落时不撞击床或其他支持物 2＝ 能对抗一些重力，但上肢不能达到或维持坐位 90°或位卧 45°，较快下落到床上 3＝ 不能抗重力，上肢快速下落 4＝ 无运动 9＝ 截肢或关节融合，解释：_____	5a 左上肢 _____ 5b 右上肢 _____
6	下肢运动： 下肢卧位抬高 30°，坚持 5 秒；对失语的病人用语言或动作鼓励，不用有害刺激。评定者可以抬起病人的上肢到要求的位置，鼓励病人坚持。仅评定患侧。	0＝ 于要求位置坚持 5 秒，不下落 1＝ 在 5 秒末下落，不撞击床 2＝ 5 秒内较快下落到床上，但可抗重力 3＝ 快速落下，不能抗重力 4＝ 无运动 9＝ 截肢或关节融合，解释：_____	6a 左下肢 _____ 6b 右下肢 _____

7	共济失调： 目的是发现双侧小脑病变的迹象。实验时双眼睁开，若有视觉缺损，应确保实验在无缺损视野内进行。双侧指鼻、跟膝胫试验，共济失调与无力明显不呈比例时记分。如病人不能理解或肢体瘫痪不记分。盲人用伸展的上肢摸鼻。若为截肢或关节融合，记录 9 分，并解释清楚。	0＝ 没有共济失调 1＝ 一个肢体有 2＝ 两个及两个以上肢体有	_____
8	感觉： 用针检查。测试时，用针尖刺激和撤除刺激观察昏迷或失语病人的感觉和表情。只对与卒中有关的感觉缺失评分。偏身感觉丧失者需要精确检查，应测试身体多处部位：上肢（不包括手）、下肢、躯干、面部。严重或完全的感觉缺失，记 2 分。昏迷或失语者可记 1 或 0 分。脑干卒中双侧感觉缺失记 2 分。无反应及四肢瘫痪者记2分。昏迷病人（1a＝3）记 2 分。	0＝ 正常，没有感觉缺失 1＝ 轻到中度，患侧针刺感不明显或为钝性或仅有触觉 2＝ 严重到完全感觉缺失，面、上肢、下肢无触觉	_____
9	语言： 命名、阅读测试。要求病人叫出物品名称、读所列的句子。从病人的反应以及一般神经系统检查中对指令的反应判断理解能力。若视觉缺损干扰测试，可让病人识别放在手上的物品，重复和发音。气管插管者手写回答。昏迷病人（1a＝3），3 分，给恍惚或不合作者选择一个记分，但 3 分仅给哑人或一点都不执行指令的人。	0＝ 正常，无失语 1＝ 轻到中度：流利程度和理解能力有一些缺损，但表达无明显受限 2＝ 严重失语，交流是通过病人破碎的语言表达，听者须推理、询问、猜测，能交换的信息范围有限，检查者感交流困难 3＝ 哑或完全失语，不能讲或不能理解	_____
10	构音障碍： 不要告诉病人为什么做测试。读或重复附表上的单词。若病人有严重的失语，评估自发语言时发音的清晰度。若病人气管插管或其他物理障碍不能讲话，记 9 分。同时注明原因。	0＝ 正常 1＝ 轻到中度，至少有一些发音不清，虽有困难，但能被理解 2＝ 言语不清，不能被理解 9＝ 气管插管或其他物理障碍，解释：_____	_____

11	忽视症： 若病人严重视觉缺失影响双侧视觉的同时检查，皮肤刺激正常，则记分为正常。若病人失语，但确实表现为关注双侧，记分正常。通过检验病人对左右侧同时发生的皮肤感觉和视觉刺激的识别能力来判断病人是否有忽视。把标准图显示给病人，要求他来描述。医生鼓励病人仔细看图，识别图中左右侧的特征。如果病人不能识别一侧图的部分内容，则定为异常。然后，医生请病人闭眼，分别测上或下肢针刺觉来检查双侧皮肤感觉。若病人有一侧感觉忽略则为异常。	0＝ 没有忽视症 1＝ 视、触、听、空间觉或个人的忽视；或对任何一种感觉的双侧同时刺激消失 2＝ 严重的偏身忽视；超过一种形式的偏身忽视；不认识自己的手，只对一侧空间定位	____
总分			____

附表 4. EQ-5D 量表

以下各项中哪项最能描述您今天的健康情况

行动

☐我可以四处走动，没有任何问题
☐ 我行动有些不便
☐ 我卧病在床

自我照顾

☐ 我能照顾自己，没有任何问题
☐ 我在盥洗、洗澡或穿衣方面有些问题
☐ 我无法自己盥洗、洗澡或穿衣

平常活动（如工作、读书、家事、家庭或休闲活动）

☐ 我能进行平常活动，没有任何问题
☐ 我在进行平常活动方面有些问题
☐ 我无法进行平常活动

疼痛/不舒服

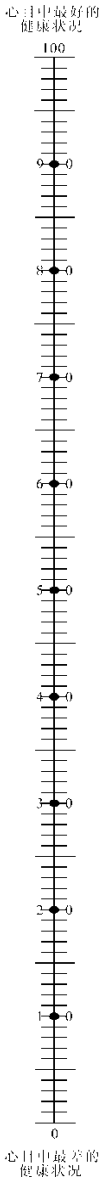
☐ 我没有任何疼痛或不舒服
☐ 我觉得中度疼痛或不舒服
☐ 我觉得极度疼痛或不舒服

焦虑/沮丧

☐ 我不觉得焦虑或沮丧
☐ 我觉得中度焦虑或沮丧
☐ 我觉得极度焦虑或沮丧

为了帮助您反映健康状况的好坏，我们画了一个刻度尺（有点像温度计），在这刻度尺上，100 代表您心目中最好的状况，0 代表您心目中最差的状况。

请在右边的刻度尺上标出您今天的健康状况。请从下面方格中画出一条线，连到刻度尺上最能代表您今天健康状况好坏的那一点。



您今天的
健康状况

问卷的完成由：

☐1 患者本人

☐2 患者在第三者的帮助下

☐3 代理人（患者的家庭成员）

附表 5: 临床重要的实验室指标异常

出血倾向	凝血酶原时间超过对照 1.5 倍或血小板计数<10×10^9/L
中、重度贫血	血红蛋白(Hb)<90g/L
肝功能异常	转氨酶超过正常 2 倍以上
肾功能异常	血肌酐>1.5mg/dl 或肌酐清除率<50ml/min

附表 6. GUSTO 出血分级标准

严重出血	包括致命性出血，原发性颅内出血，创伤后症状性颅内出血，或需要输血、输液、使用缩血管药物和需要外科介入的出血
中等量出血	需要输液但未达到严重出血的标准；包括血红蛋白/红细胞压积绝对降低，造成严重残疾，伴有严重视野缺损的眼内出血等
少量出血	包括穿刺部位出血、血肿等

附录Ⅰ：

研究方案修改版本 1.0（2009 年 1 月 3 日）至版本 1.1（2009 年 2 月 25 日）

✧ 剂量方案（第 23 页）：所有“第 2 天到第 30±7 天”均改为“第 2 天到第 21（±2）天”。所有“从第 31±7 天”均改为 “第 21（±2）天”。

✧ 研究流程（第 30 页）：删除出院访视，第 30 天访视被改为第 21 天访视。

附录Ⅱ：

研究方案修改版本 1.1（2009 年 2 月 25 日）至版本 1.2（2009 年 3 月 15 日）

✧ 10.1.1 样本量估计(10.1.1.1 主要无效假设, 32 页; 10.1.1.1.6 检验功效和第一类错误, 35 页):用 80%的检验功效检测相对危险度降低 22%改为用 90%的检验功效。所以，样本量以 5100 代替 3800。

附录Ⅲ:

研究方案修改版本 1.2（2009 年 3 月 15 日）至版本 1.3（2009 年 5 月 20 日）

✧ 研究目的（3.2 次要研究目的，16 页）：增加 2 个亚组。

3.2.11 比较不同随机化时间（小于 12 小时对比大于 12 小时）两种治疗方案的有效性和安全性差异。

3.2.12 评估有或没有最初头 CT 或 MRI 影像梗死的证据患者的主要终点事件和颅内出血事件的发生率。

✧ 中心数:在全国临床研究网络招募大约 80 家分中心改为大约 100 家分中心。

✧ 7.4.2 可以允许的伴随治疗（26 页）：应当避免质子泵抑制剂（如奥美拉唑等）与氯吡格雷药物之间的相互影响，因此补充下列内容：由于不确定泵抑制剂（如奥美拉唑等）与氯吡格雷药物之间存在相互影响，因此既往服用质子泵抑制剂的患者应使用其他药物进行替换（如 H2 受体抑制剂），需要治疗的患者应优先使用 H2 受体抑制剂等药物而尽量避免使用质子泵抑制剂。

同样，与氯吡格雷有相互作用的药物都应该尽量避免使用，这些药物包括：艾美拉唑（耐信）、西咪替丁（包括处方和非处方药物）、氟康唑（大扶康）、酮康唑（里素劳片）、伏立康唑（威凡）、依曲韦林、非尔氨酯、氟西汀（百优解, 奥氮平氟西汀）、氟伏沙明（兰释）。

附录Ⅳ：

研究方案修改版本 1.3（2009 年 5 月 20 日）至版本 1.4（2009 年 7 月 25 日）

✧ 4.3 研究组织（18 页）：

- 筹划指导委员会增加王晨教授
- 执行委员会成员增加：王拥军，Claiborne Johnston（美国），王伊龙，赵性泉，刘丽萍，孟霞，王安心，林金嬉。
- DSMB 成员由李昊，王伊龙，周永改变为李昊，沈海鹏，王伊龙，王安心，刘改芬，王献伟，潘岳松。
- 裁决委员会增加：Lawrence. Wong (香港), David Wang (美国), James Wang (美国).