ORIGINAL RESEARCH ARTICLE

Initial 3-Weeks' Apixaban Versus Dual-Antiplatelet Therapy (Clopidogrel and Aspirin) Followed by Clopidogrel Alone in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events (ADANCE): Study Protocol for a Randomized Controlled Trial

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Abstract

Background Nondisabling cerebrovascular events represent the largest group of cerebrovascular disease with a high risk of recurrent stroke. A recent trial demonstrated that dual-antiplatelet therapy (clopidogrel and aspirin), compared with aspirin monotherapy, reduced the risk of recurrent stroke and was not associated with increased risk of hemorrhagic events. Apixaban, a new oral anticoagulant, has been proven to be as safe and effective as traditional anticoagulants while carrying significantly less risk of intracranial hemorrhage. Patients with transient ischemic attack (TIA)/minor stroke might benefit from apixaban treatment; therefore, an adequately powered randomized study is needed.

Methods and Results The ADANCE [Apixaban Versus Dual-antiplatelet Therapy (Clopidogrel and Aspirin) in Acute Non-disabling Cerebrovascular Events] study is a randomized, double-blind clinical trial with a target enrollment of 5,500 patients. A 21-day regimen of apixaban or of clopidogrel with aspirin followed by clopidogrel on days 22 through 90 will be administered to randomized participants with acute TIA or minor ischemic stroke. The primary efficacy endpoint is the percentage of patients with any new stroke (ischemic or hemorrhage), including fatal stroke, at day 21. Study visits will be performed on the day of randomization, and at days 7, 22, and 90.

Discussion The novel oral anticoagulant apixaban has been widely used with fewer adverse effects than traditional anticoagulants. We designed the ADANCE trial to observe the effects of apixaban on recurrent stroke after TIA or minor stroke. The results should better guide the selection of anticoagulant or dual-antiplatelet therapy for patients with acute TIA or minor ischemic stroke.

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1 Introduction

Stroke, the leading cause of acquired disability, affects 15 million people worldwide every year [1]. Transient ischemic attack (TIA) and acute minor ischemic stroke, defined as a National Institutes of Health Stroke Scale (NIHSS) score ≤3, represent the largest group of cerebrovascular disease. About 30–40 % of patients with ischemic stroke have had a prior TIA or minor stroke [2]. A previous study suggests that the 90-day risk of a subsequent stroke is 10.5 % after TIA and that almost half of these strokes could occur within the first 2 days [3]. After a

minor stroke, the risk of recurrence is as high as 18.5 % at day 90 [4].

Aspirin, the gold standard of medical care for antiplatelet therapy, has been used most extensively for ischemic cerebrovascular diseases. Compared to intravenous tissue plasminogen activator (t-PA), which has a narrow therapeutic window (up to 4.5 h after symptom onset) [5], and traditional anticoagulants with a higher risk of bleeding events, aspirin has a modest effect on acute ischemic stroke. Compared to placebo, aspirin administration shows a slight increase in the risk of cerebral hemorrhage. The recently published CHANCE (Clopidogrel in High-risk Patients With Acute Non-disabling Cerebrovascular Events) study [6] reported superior results with dual-antiplatelet therapy (DAPT), i.e., superiority of clopidogrel–aspirin over aspirin monotherapy. DAPT was not associated with increased hemorrhage events. The results shed light on the benefits of exploiting more effective medical therapy for patients suffering non-disabling cerebrovascular diseases.

Traditional anticoagulants have been used to lower the risk of early recurrent stroke; however, the benefit is negated by an increasing rate of bleeding complications [7, 8]. Recently, the novel oral anticoagulants have received extensive attention because of the following advantages [9]: (1) they directly target the coagulation cascade with rapid onset/offset of action; (2) fewer adverse effects (especially lower rates of major hemorrhage); (3) lower risk for drug–drug interactions; and (4) a more predictable response. Apixaban, a direct factor Xa inhibitor, as one of these novel oral anticoagulants, has been approved for preventing venous thromboembolism after elective hip or knee replacement in Europe [10] and for reducing the risk of stroke and dangerous blood clots (systemic embolism) in patients with atrial fibrillation (AF) by the US Food and Drug Administration [11]. The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial [12] found that apixaban could reduce the risks of systemic embolism, bleeding events, and all-cause mortality, with better tolerability in patients with AF, compared with warfarin treatment. The AVER-ROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial [13] confirmed that apixaban was associated with more effective reduction of stroke and a similar risk of major bleeding compared with aspirin in patients with AF. Hence, we speculated that apixaban might show better effect on patients with TIA or acute ischemic stroke.

To date, the effect of apixaban versus DAPT (clopidogrel and aspirin) on acute non-disabling cerebrovascular disease is still unconfirmed. In the ADANCE study, we will enroll patients with TIA and minor ischemic stroke who are showing particularly high risk for recurrent ischemia, low risk for hemorrhage, and relatively stable systematic conditions after cerebrovascular event onset. The study was designed to estimate whether apixaban administration is superior to DAPT, in order to decrease recurrent stroke in Chinese patients after TIA and acute minor stroke.

2 Study Objective

An initial 3 weeks of apixaban versus DAPT therapy (clopidogrel and aspirin) followed by clopidogrel alone in high-risk patients with acute non-disabling cerebrovascular event (ClinicalTrials.gov identifier NCT01924325) is a randomized, double-blind, multicenter, controlled clinical trial enrolling 5,500 Chinese patients with acute TIA or minor stroke. The primary objective of the trial is to determine whether apixaban is safe and could reduce the risk of any stroke (both ischemic and hemorrhagic) when initiated within 24 h of symptom onset in high-risk patients with TIA or minor ischemic stroke as compared with DAPT.

3 Study Participants

In total, 5,500 patients will be recruited through 100 emergency departments in general hospitals in China. Two subtypes of patients will be enrolled: (i) acute non-disabling ischemic stroke; and (ii) acute TIA. Ischemic stroke is defined as an abrupt onset of a neurologic deficit that is attributable to acute occlusion of an intracranial vessel. The standard definition of TIA requires that all neurologic signs and symptoms resolve within 24 h, regardless of whether there is imaging evidence of new permanent brain injury; stroke has occurred if the neurologic signs and symptoms last for >24 h, with image evidence of a new brain infarction. Informed consent will be supported by a patient (or next of kin) information leaflet in Chinese. A consultation meeting will be developed by a study physician to ensure patients and their families understand the study procedure and consent to participation in the trial [14].

The study has been approved by the Medical Ethical Reviewing Committee of the Fourth Military Medical University Medical Center, Xi'an, China. 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 International Conference on Harmonization guidelines for Good Clinical Practice.

4 Study Population and Procedures

Table 1 shows the inclusion and exclusion criteria of the ADANCE trial.

Figure 1 shows the trial procedure. Participants with suspected TIA or minor stroke will first receive a head computed tomography (CT) to exclude the intracranial hemorrhage and optional head magnetic resonance imaging (MRI) + diffusion weighted imaging (DWI) to confirm the area of infarction. A certified, trained, licensed physician investigator will be required to confirm the diagnosis of TIA or minor ischemic stroke and to calculate the ABCD^2 (age, blood pressure, clinical features, duration of TIA, and presence of diabetes) score for subjects with TIA or the NIHSS score for subjects with minor stroke. Once a standardized, structured interview is performed, the data will be recorded in the case report form for each patient. All clinical data, biological samples, and radiological images will be sent to the central study site where a cerebrovascular neurologist will review the data. Demographic, medical, social, and behavioral variables will be determined along with baseline medications. Anthropometry will be conducted with standardized equipment calibrated on a daily basis.

Patients meeting these criteria and offering informed consent will be randomized, and the first dose of study medication will be given within 24 h of symptom onset.

Patients will be randomized into two groups:

1. Receiving a 75 mg dose of clopidogrel and 75 mg dose of aspirin from day 1 to day 21, with placebo apixaban twice daily.
2. Receiving apixaban 5 mg twice daily, with placebo clopidogrel and placebo aspirin from day 1 to day 21.

A reduced dose of apixaban (2.5 mg twice daily) will be administered if patients have two or more of the following three factors: advanced age ≥80 years, elevated serum creatinine ≥1.5 mg/dL, and low body weight ≤60 kg.

From day 22 to day 90, all patients will receive a 75 mg dose of clopidogrel long-term antiplatelet therapy. Study visits will be performed at the day of randomization, and at days 7, 22, and 90. From randomization to follow-up visits, the following information will be collected: a neurologic evaluation [modified Rankin Scale (mRS) and NIHSS]; a

Table 1 Inclusion and exclusion criteria

Inclusion criteria

  Adult subjects (male or female ≥18 years old)

  Acute non-disabling ischemic stroke (NIHSS ≤3 at the time of randomization) that can be treated with study drug within 24 h of symptom onset. Symptom onset is defined by the 'last see normal' principle

  TIA (neurologic deficit attributed to focal brain ischemia, with resolution of the deficit within 24 h of symptom onset) that can be treated with investigational medication within 24 h of symptom onset. 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, on baseline head CT or MRI scan

  mRS score >2 at randomization (pre-morbid historical assessment)

  NIHSS ≥4 at randomization

  Clear indication for anticoagulation (atrial fibrillation, mechanical cardiac valves, deep venous thrombosis, pulmonary embolism, or known hypercoagulable state)

  Contraindication to investigational medications

  Thrombolysis for ischemic stroke within preceding 7 days

  History of intracranial hemorrhage

  Current treatment (last dose given within 10 days before randomization) with heparin therapy or oral anticoagulation

  Gastrointestinal bleed or major surgery within 3 months

  Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months

  TIA or minor stroke induced by angiography or surgery

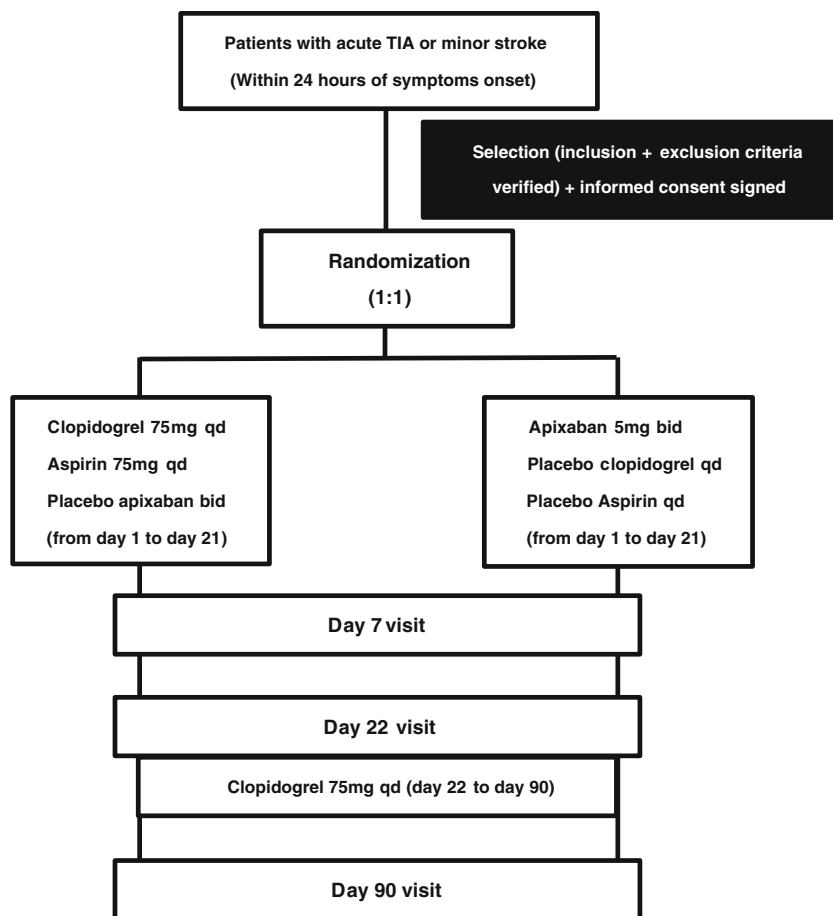 Severe non-cardiovascular co-morbidity with life expectancy <3 months

  Women of child-bearing age not practicing reliable contraception who do not have a documented negative pregnancy test result

  Severe renal failure, defined as GFR ≤30 mL/min or serum creatinine ≥4 mg/dL

  Severe hepatic insufficiency (Child-Pugh score B to C)

CT computed tomography, *GFR* glomerular filtration rate, *MRI* magnetic resonance imaging, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *TIA* transient ischemic attack

Fig. 1 Flowchart outlining the trial protocol. *bid* twice daily, *qd* once daily, *TIA* transient ischemic attack


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│   Patients with acute TIA or minor stroke    │
│   (Within 24 hours of symptoms onset)        │
└─────────────────────────────────────────────┘
              ┌─────────────────────────────────────────────┐
              │ Selection (inclusion + exclusion criteria    │
              │ verified) + informed consent signed          │
              └─────────────────────────────────────────────┘
              ┌─────────────────────────────────────────────┐
              │   Randomization                              │
              │   (1:1)                                      │
              └─────────────────────────────────────────────┘

┌──────────────────────────┐      ┌──────────────────────────┐
│ Clopidogrel 75mg qd       │      │ Apixaban 5mg bid          │
│ Aspirin 75mg qd           │      │ Placebo clopidogrel qd    │
│ Placebo apixaban bid      │      │ Placebo Aspirin qd        │
│ (from day 1 to day 21)    │      │ (from day 1 to day 21)    │
└──────────────────────────┘      └──────────────────────────┘

              ┌─────────────────────────────────────────────┐
              │   Day 7 visit                                │
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              │   Day 22 visit                               │
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              ┌─────────────────────────────────────────────┐
              │ Clopidogrel 75mg qd (day 22 to day 90)       │
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              ┌─────────────────────────────────────────────┐
              │   Day 90 visit                               │
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physical examination, including measurement of weight (in kg) and vital signs (supine systolic and diastolic blood pressure, heart rate); a neurological dysfunctions assessment; concomitant medications; and adverse events. For ensuring the safety of patients during the study, the trial should be stopped in the following conditions: (i) the rate of intracranial hemorrhage exceeds 5 % or the rate of other hemorrhagic events is more than 10 %; or (ii) the rate of 90-day stroke recurrence (ischemic or hemorrhagic) in the DAPT group is 20 % less than in the apixaban group.

An individual not associated with the trial will use a computerized random number generator to randomly assign subjects to group. Allocation concealment will be ensured by using an opaque, sealed envelope containing the group assignment.

5 Study Outcomes

The primary efficacy endpoint is the percentage of patients with any new stroke (ischemic or hemorrhage), including fatal stroke, at day 21.

Secondary efficacy endpoints include the following:

1. The percentage of patients at day 90 with new clinical vascular events [ischemic stroke/hemorrhagic stroke/TIA/myocardial infarction (MI)/vascular death] as a cluster and evaluated individually;
2. mRS score changes given as a percentage with a score of 0–2 versus 3–6 at day 90;
3. Changes in NIHSS scores at day 90; and
4. Efficacy endpoints will also be analyzed stratified by etiologic subtypes (non-intracranial artery diseases vs. intracranial artery diseases), time randomization (<12 vs. ≥12 h), qualifying event (TIA vs. minor stroke), and age (dichotomized at a 5-year cut-point closest to median age).

Safety endpoints include the following:

1. Moderate to severe bleeding events at day 90, according to the GUSTO (Global Utilization of Streptokinase and T-Pa For Occluded Coronary Arteries) definition, including fatal bleeding and symptomatic intracranial hemorrhage, and incidence of symptomatic and asymptomatic intracranial hemorrhagic events at day 90;
2. Total mortality (for any reason) at day 90; and

3. Adverse events/severe adverse events reported by the investigators.

6 Randomization, Allocation Concealment, and Blinding

Subject numbers are to be assigned sequentially as each patient enters the study. After informed consent is received, patients fulfilling the inclusion criteria will be randomized by computer-generated random numbers (Microsoft Excel[®] 2010, Microsoft Corporation, Redmond, WA, USA) at the statistics research office of the Fourth Military Medical University. A clinical research associate will make opaque blinded envelopes (with consecutive numbers) and deliver them to each participating center. Random allocation is to be performed within 24 h after a patient is enrolled. The block size and treatment-assignment table would not be available to the researchers until the end of the trial.

The study medication would be stored under the conditions specified on the label in a locked, safe area of the pharmacy department to prevent unauthorized access. Both the study medication and the placebo will be indistinguishable; they will be manufactured by the same company with similar appearances, organoleptic characteristics, and presentations.

In the event of an emergency, an investigator and a clinical pharmacist would decide whether it is necessary to unblind the subject's treatment assignment with the unblinding envelopes provided to the hospital. If unblinding were necessary, the investigator must record the reason, as well as the date and time of the event. In each participating center, an independent researcher would be assigned to collect the trial paper and electronic records. In the central trial coordinating office, an independent research assistant would have access to all unblinded data and maintain confidentiality of patient records.

7 Statistical Considerations

The primary null hypothesis of this trial is as follows: in patients with TIA or minor ischemic stroke treated with clopidogrel and aspirin, there is no difference in 90-day risk of stroke (ischemic or hemorrhagic) in those treated with a 21-day regimen of apixaban 5 mg twice daily, if therapy is initiated within 24 h 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. According to previous clinical studies [4, 15, 16], the 90-day risk of stroke recurrence in the placebo (aspirin) group is about 14 % among high-risk TIA (ABCD^2 score $\geq$4) or minor stroke patients treated with aspirin within 24 h of symptom onset. The CHANCE study [6] further indicated that, as compared with aspirin monotherapy, clopidogrel and aspirin treatment reduced the risk of recurrent stroke by 32 % and was not associated with increased hemorrhage events. The results from our preliminary study were used to calculate the sample size (unpublished data). The ratios of the 90-day stroke recurrence in the DAPT group and apixaban group were 10.47 and 7.96 %, respectively. Therefore, we presume that the 90-day risk of stroke recurrence is 10.5 % among high-risk TIA or minor stroke patients with clopidogrel–aspirin therapy within 24 h of symptom onset. A relative risk reduction of 24 % (relative risk with addition of apixaban is 0.76) is the smallest difference we will attempt to detect. The following equation was used for calculating the sample size:

$$n = 2\lambda \left/ \left(2\sin^{-1}\sqrt{p1} - 2\sin^{-1}\sqrt{p2}\right)^2 \right.$$

With a two-sided 5 % significance level (α) and an 80 % power ($1-\beta$), $p1$ of 0.105, $p2$ of 0.08, and $\lambda_{0.05,\,2}$ of 9.63, the minimal sample size per group was estimated to be 2,600 patients. About 5,500 participants in total in the two groups is the final estimated sample size with 5 % withdrawals (medication non-adherence). 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 before loss to follow-up).

All analyses will be intent to treat. In these analyses, we will compare apixaban versus DAPT treatment. Kaplan-Meier estimates of the cumulative risk of a stroke (ischemic or hemorrhagic) event during a maximum of 90 days' follow-up, with hazard ratios and 95 % confidence intervals calculated using a Cox proportional-hazards model and the log-rank test to evaluate the treatment effect will be reported. The Chi-square test of association will be used to compare groups at baseline as appropriate. Logistic regression is to be used to determine the significance of the results obtained. All statistics would be two-sided with $p < 0.05$ considered significant.

8 Study Organization

The progress of the study would be monitored by the Data and Safety Monitoring Board (DSMB) to ensure the high standards of ethics and patient safety. The DSMB would monitor the trial via scheduled and unscheduled reviews, supervise stopping rules and unmasking, and maintain the

confidentiality of internal discussions and validity of the reports.

An Executive Committee meeting would be organized to make major decisions. Quality control inspectors are responsible for inspecting the quality of research sites and study data periodically, supervising any quality problem during the trial, and reporting to the Executive Committee. The members of the Steering Committee, including two project directors, will be members of the Executive Committee and will convene monthly (teleconferences or physical meetings) to review the status of the trial and available blinded data; they will take appropriate action regarding the conduct of the study.

An Adjudication Committee charter including membership, role, and responsibilities is to be approved before the start of the trial by the Adjudication Committee and the Executive Committee. This committee will be composed of Academic Members, including an independent statistician, who are not otherwise participating in the trial.

9 Discussion

Acute non-disabling cerebrovascular events are common and often portend a disabling stroke. Recently, a few effective therapies have been established according to clinical trials. Aspirin is the mainstay antiplatelet therapy that has been used in patients with an acute cerebrovascular events [17] for a long time. Clopidogrel, a platelet adenosine diphosphate receptor antagonist, has been shown to be as effective for secondary stroke prevention as aspirin, with a similar rate of ischemic stroke, MI, or vascular death [18]. Clopidogrel could not produce maximal inhibition of platelet aggregation in a conventional dose (75 mg/day) for 5 days [19]. This delay presents a problem for an early treatment effect in the management of patients with acute ischemic stroke. Recently, DAPT indicated a reduced risk of recurrent stroke and an acceptable risk of hemorrhage events for high-risk patients with non-disabling cerebrovascular events [6]. Therefore, we can't deny the possibility that there may have been some other medical regimen that could improve outcomes in those patients.

Patients administered with traditional anticoagulants immediately after acute ischemic stroke onset have been reported to have a lower risk of recurrent stroke and an increased rate of bleeding complications, as compared with untreated patients or patients who received an antiplatelet agent [20, 21]. However, in recent times, novel oral anticoagulants, including direct factor Xa inhibitors and direct thrombin inhibitors, have shown advantage in reducing the risk of stroke in patients with AF [11, 22] and preventing or treating venous thromboembolism [10] with fewer hemorrhagic adverse effects and a preferable response compared with traditional anticoagulants [9]. Recently, apixaban (a direct factor Xa inhibitor) has received broad attention for its reliable anticoagulant effect and lower rates of major hemorrhage [23]. Compared with warfarin, apixaban shows better tolerability and a lower rate of systemic embolism, bleeding events, and all-cause mortality [12]. Compared with aspirin, apixaban has been found to have a similar risk of major bleeding and reduced risk of stroke onset in patients with AF [13]. However, the effects of apixaban on the early recurrent stroke risk after TIA and acute minor stroke are still uncertain. The ADANCE trial is a randomized, double-blind, multicenter controlled clinical trial in China. We will assess the effect of a 3-month regimen of apixaban treatment for the first 21 days followed by clopidogrel monotherapy versus a 3-month regimen of DAPT for the first 21 days followed by clopidogrel alone, on reducing the 3-month risk of any stroke when initiated within 24 h of symptom onset in high-risk patients with TIA or minor stroke.

Author contributions ZG: the principal investigator for this project who led the conceptualization, design, and funding applications, and made strategic decisions for this research protocol. YF and LH: co-led the conceptualization, design, development, and implementation of this research protocol and contributed to the writing of this manuscript. JWR: led the development of the data management protocol and statistical analysis plan. HJL and JW: contributed to the design, development, and implementation of this research protocol. All authors read and approved the manuscript.

Trial status The trial has not yet begun to enroll patients. The trial is expected to enroll patients in January 2015.

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