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Study protocol for aspirin plus rivaroxaban efficacy and safety in embolic stroke of undetermined source: A randomized, placebo controlled, outcome assessor blind, feasibility study

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Abstract

Background & Objectives: Despite recent scientific advances in acute ischemic stroke treatment, there has been limited progress for the secondary prevention of cryptogenic ischemic stroke. The present proposed study is designed for evaluation of efficacy and safety of rivaroxaban plus aspirin in reducing stroke recurrence in patients with embolic stroke of undetermined source (ESUS). *Methods:* This is a randomized, parallel-group, outcome assessor blind, placebo-controlled study on the recent (7-60 days) ESUS patients identified only one risk factor of potential embolic source. After meeting all inclusion and exclusion criteria patients will be randomized to rivaroxaban 2.5 mg BID plus ASA 80 mg daily or ASA 80 mg plus placebo (1:1 ratio) and will be visited every three months until one year. Any adverse events, serious side effects, outcome events will be recorded. *Results:* The primary outcome is defined as the rate and time of stroke occurrence and major bleeding events.
Conclusions: Low dose rivaroxaban plus aspirin is expected to be a safe and effective for prevention of recurrence in ESUS.

Keywords: Embolic stroke of undetermined source, cryptogenic stroke, direct oral anticoagulants, recurrence, antiplatelet

INTRODUCTION

Cryptogenic stroke encompasses for about 25% of ischemic strokes, which is one of the most common neurological diseases associated with high mortality and morbidity.[1-4] Literature evidence demonstrated that most cryptogenic strokes have an embolic source; therefore, in 2014 CS /ESUS International Working Group construct a new clinical term, embolic stroke of undetermined source (ESUS) defined as non-lacunar stroke on cerebral imaging in the absence of the extra or intracranial atherosclerosis causing ≥50% luminal stenosis in relevant artery, major-risk cardioembolic source of embolism and any other specific cause of stroke.[5-7] Approximately 17% of all patients with ischemic stroke are classified as having ESUS, which is associated with 5% per year rate of stroke recurrence.[1,8] Despite recent therapeutic advances in acute ischemic stroke treatment, there has been limited progress for the secondary prevention of cryptogenic ischemic strokes in recent decades.[9]

One of the main pathophysiologic mechanism for thrombogenesis regarding some risk factors of ESUS is low blood flow, which predisposes to formation of thrombi that may respond better to anticoagulation.[8,10] On the other hand, for other embolic sources, like aortic and non-stenotic carotid atherosclerosis, the ulceration of a plaque triggers the formation of thrombi that may respond better to antiplatelet.[8,11] In this situation, it may be hypothesized that treating ESUS patients with anticoagulants rather than aspirin would just result in exchanging the type of thrombi, while the overall burden remaining largely unchanged.[8] If this hypothesis is correct, simultaneous inhibition of both site of thrombi with a combination of anticoagulation and antiplatelet would be associated with a significant reduction of stroke recurrences in patients with ESUS.[8] But it is still some concern about increased risk of bleeding. For this reason, we choose low dose of rivaroxaban, that its safety and efficacy has been proved in COMPASS study.[11]

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The rationale of ASA Plus Rivaroxaban Efficacy and Safety Trial in Embolic Stroke of Undetermined Source (AREST-ESUS) is to evaluate the effects of early oral anticoagulation with low dose of rivaroxaban plus ASA vs. antiplatelet therapy with ASA alone on prevention of ischemic stroke recurrence in ESUS and also its safety assessment.

METHODS

Study design

The AREST-ESUS is a prospective, randomized, parallel- group, outcome assessor blind, placebo-controlled feasibility study. This study is intended to show whether patients given rivaroxaban plus ASA have fewer thrombosis in the brain vasculature with no risk of major bleeding. The study protocol and related documents have been approved by the institutional review board and ethics committee board of Mazandaran University of Medical Sciences (Reference number: IR.MAZUMS.REC.1399.454 at 2020-07-08) and registered in Clinicaltrials.gov (NCT04273516) and IRCT.ir (IRCT20200112046094N1).

This study is conducted in accordance with the Helsinki Declaration as revised in 2013. Written informed consent will be obtained from all subjects prior to the randomization.

Participant eligibility

The AREST-ESUS study will be conducted in Bou-Ali Sina hospital in Sari, Iran. Adult patients (age ≥ 18 years) with recent ischemic stroke (7-60 days) and, according to ESUS criteria which is defined as: stroke detected by computed topography (CT) or MRI that is not lacunar, without any extra-cranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying at the area of ischemia, no major-risk of cardio-embolic sources of embolism and no other specific cause of stroke; individuals who fulfilled all eligibility criteria (table 1) will be recruited.

Table 1: Eligibility criteria

Inclusion criteria
Diagnosis of ESUS
Recent stroke during 7-60 days
Patient age>18
Written informed consent
Only one risk factor of potential embolic source including:
1-PTFV1 in standard ECG ≥0.05 mm.s or ≥0.005 mv.s
2-LVH in standard ECG(Sokolow index≥ 35 mm) or echocardiography
3-Moderate or severe MR, AR or AS on echocardiography
4-left atrium enlargement on echocardiography
5-PFO not candidate for closure
Exclusion criteria
History of hypersensitivity to the investigational medicinal product
Indication for anticoagulation
Indication for dual antiplatelet therapy
Contraindication to investigational medications
History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intraarticular bleeding
Gastrointestinal bleeding or major surgery within 3 months
Planned or likely revascularization(any angioplasty or vascular surgery)within the next 3 months
HAS-BLED score > 3
Severe non-cardiovascular comorbidity with life expectancy < 3 months
Severe renal failure, defined as GFR<15ml/min, Dialysis, transplant, Cr >2.26 mg/dL
Severe hepatic insufficiency, Cirrhosis or Bilirubin >2x Normal or AST/ALT/AP >3x Normal
Modified Rankin Scale of >=4
Inability to swallow medications
Hemorrhagic transformation of brain infarction
Radiological or microbiological evidence of COVID-19 infection

Intervention

All patients will receive standard treatment of ischemic stroke during hospital admission. Patients in intervention group will take aspirin (enteric-coated tablet) 80 mg once daily plus rivaroxaban (film-coated tablet) 2.5 mg twice daily and in comparator group will take aspirin (film-coated tablet) 80 mg once daily plus placebo twice daily. Mean patient follow-up is expected to be about one year, but the study will be continued until all patients recruit. Participants will be monitored by phone contact every one month, in addition, they will be visited in person at month 3, 6, 9 and 12 of the study, until the end of study date (Figure 1). In each visit session, participants will be assessed for adherence, any adverse effect, vital signs, and occurrence of safety concerns or efficacy outcomes events. During the follow up period, if any new events such as stable angina, paroxysmal or overt AF; that need dual antiplatelet or higher dose of anticoagulation, the study drugs will be stopped. The drugs will be prescribed for approximately 3 months for each patients to use. In each visit, patients will be evaluated by neurologist and the adherence of patients checked by pill counting.

Randomization and blinding

Patients will be randomized in a 1:1 fashion to intervention or comparator group. A list of random numbers generated by using a permuted-block randomization method with 4 block size and anonymized patient list encoded. The codes will be written on a sealed envelope and the group type (intervention or comparison) will be placed on paper inside the envelope. These envelopes are stacked in order. At the time of enrollment of each patient who met the inclusion and exclusion criteria, the upper envelope will be removed, and based on the code inside, it is determined which group it belongs to intervention or placebo group. A neurologist will give drugs or placebo according to randomized code. This study is designed as outcome assessor blind, so neurologist who assess patients outcome will be blind.

Primary and secondary outcomes

The primary efficacy outcome is the time to and rate of stroke occurrence. The primary safety outcome is the major bleeding according to the criteria of the International Society of Thrombosis and Hemostasis[12]. The secondary

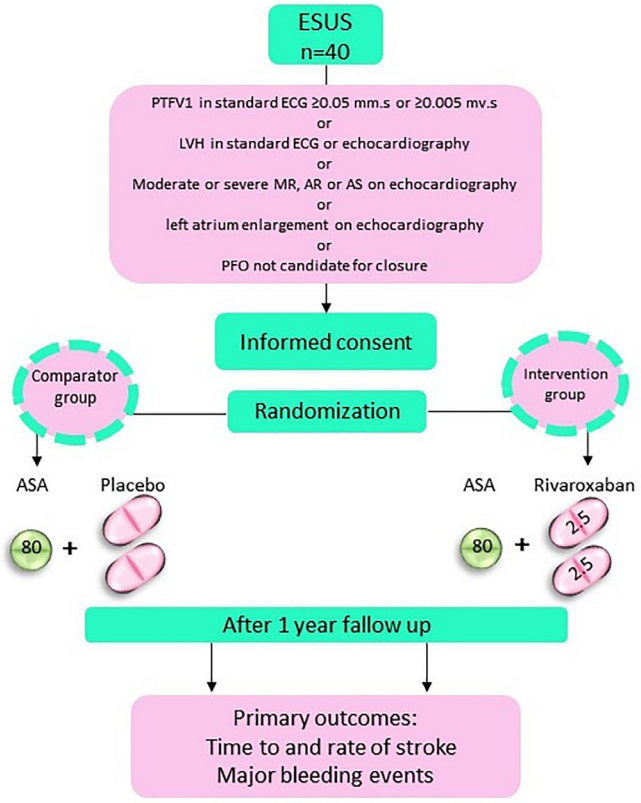

Figure 1. Study design

outcomes are defined as all-cause of mortality, any systemic embolism, any cardiovascular events, any cardiovascular death, non-major bleeding, intracranial and fatal bleeding.

Safety profile

If any hemorrhagic event occurs during fallow up, the patients will be treated accordingly and the drugs will be stopped. In non-major bleedings, the drugs will be discontinued temporarily and then resume whenever possible. However, in case of major bleeding, it will be the safety end point of study and the study drugs will be stopped without any re-challenges.

Statistical analysis

By considering the limited data about anticoagulation after ESUS and the effects on the chosen endpoint, unknown rate of ESUS and limited enrolling center (only one site in a small city), we design a feasibility study, thus considered 20 patients in each arm. The primary efficacy and safety analyses will be based on the intent-to-treat population. Aspirin plus rivaroxaban assigned patients will be compared with the aspirin control group using a log–rank test. Data will be expressed as mean, standard deviations and 95% confidence interval. Group difference will be estimated using one-way ANOVA. The level of significance set as $p<0.05$.

DISCUSSION

Since years ago the use of vitamin k antagonist as main oral anticoagulant, has been tried for cryptogenic stroke patients, however, due to its hemorrhagic complications, there is reservation in the recommendation of their use[7].

To date, limited studies have been performed on the use of direct oral anticoagulants (DOACs) regarding their efficacy and safety profile.[9] According to DOACs effects on prevention of embolic stroke in AF patients[13], anticoagulants have been hypothesized to be more efficient than antiplatelet drugs for secondary prevention following ESUS. So various randomized trials designed at reducing recurrent stroke in ESUS with DOACs. NAVIGATE-ESUS compared rivaroxaban 15 mg daily with ASA.[14] This study terminated early because of increased risk of bleeding in the rivaroxaban arm without the benefit of lower risk of stroke/systemic embolism.[14] In RESPECT-ESUS dabigatran was used; this study was also terminated after interim analysis showed dabigatran was not superior to aspirin in preventing recurrent stroke.[15] ATTICUS[16] and ARCADIA[17] are still in progress to examine the apixaban. COMPASS study evaluated rivaroxaban given alone or in combination with aspirin as an alternative to aspirin monotherapy for the prevention of vascular events in patients with stable coronary artery or peripheral artery disease.[18] This study showed that a combination of low-dose rivaroxaban and aspirin was associated with a large reduction of stroke risk compared with aspirin as monotherapy; with no significant difference in intracranial or fatal bleeding between these two groups.[19] As regards to COMPASS study[18,19] results, a new hope arose. Thus, it is hypothesized that combination therapy with low dose of anticoagulants and antiplatelets may be better than either alone for stroke prevention in ESUS.

In conclusion, the result of AREST-ESUS study may propound more information on anticoagulant plus antiplatelet therapy in ESUS patients for prevention of recurrent ischemic stroke and provide feasibility of a larger multi-centric study in future.

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DISCLOSURE

Conflicts of interest: None

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