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Original article

Design and rationale of the STroke secondary prevention with catheter ABLation and EDoxaban clinical trial in patients with non-valvular atrial fibrillation: The STABLED study

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ABSTRACT

Background: Catheter ablation (CA) has been reported to reduce risk of stroke in patients with nonvalvular atrial fibrillation (NVAF) in retrospective studies. However, the risks and benefits of CA have not been well elucidated in patients with NVAF and who have suffered a recent ischemic stroke in prospective randomized trials. Thus, the aim of the STABLED clinical trial is to investigate the efficacy and safety of CA with anticoagulant therapy using edoxaban in patients with NVAF and a history of recent ischemic stroke.

Methods and design: The STABLED trial is a multicenter, prospective, randomized, open-label, standard medication-controlled study in Japan. The target patient number is 250, comprising 125 patients receiving standard medication and 125 receiving CA. For patients allocated to the CA group, ablation is to be performed between 1 to 6 months from the onset of index stroke. The observation period will be 3 years from the day of random allocation of the final patient to any of the groups. The primary outcome measure is the composite of recurrence of ischemic stroke, systemic embolism, all-cause death, and hospitalization for heart failure.

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Conclusion: This study will investigate the effectiveness and safety of CA and basic anticoagulation treatment with edoxaban for patients with NVAF who have suffered a recent ischemic stroke. The aim is to determine the best evidence for an optimal treatment strategy for patients with NVAF and recent stroke.

Trial registration: UMIN000031424/NCT03777631.

Introduction

Atrial fibrillation (AF) is a primary risk factor for ischemic stroke, and 1 in 5 cases of ischemic stroke is associated with AF [1]. AF-associated stroke is often severe, and related to high mortality and severe morbidity [2]. Therefore, to prevent stroke due to AF is crucial, for both primary and secondary prevention.

In patients with AF, stroke is an independent risk factor for a subsequent ischemic stroke [3]. Although anticoagulant therapy can effectively reduce thromboembolic events [4,5], the reported annual recurrence rate in non-valvular AF (NVAF) and previous stroke patients in the "real-world" is not low even with appropriate antithrombotic treatment; 8.6% in patients with "guideline adherent" antithrombotic therapy [6] and around 5% in patients treated with anticoagulant therapy [7]. Patients with NVAF and recent stroke are a high-risk population for stroke recurrence even with anticoagulant therapy, and developing an optimal secondary prevention strategy is important.

Catheter ablation (CA) is now widely used to treat symptoms related to NVAF. Some retrospective studies showed a beneficial effect of CA for stroke prevention using age-/sex-matching [8] or propensity-score matching [9]. Moreover, CA has the potential to improve survival [10] or prevent heart failure development in patients with AF [9,11]. However, the effect of CA for secondary stroke prevention or the impact of CA for NVAF patients with recent ischemic stroke on survival or heart failure development has not been evaluated in a prospective randomized trial. Therefore, in the present study, we intend to compare two groups of patients with NVAF with a history of ischemic stroke: a group receiving standard medical therapy (control group) and a group receiving standard medical therapy plus CA (CA group).

Methods

Study design

The STroke secondary prevention with catheter ABLation and EDoxaban (STABLED) clinical trial is a multicenter, randomized, open-label, parallel group study comparing standard medical therapy (control group) alone, or combined with CA (CA group). The study will involve 37 medical centers across Japan, and will be performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH), Harmonised Tripartite Guideline on Good Clinical Practice (GCP), and Clinical Trials ACT in Japan. Approval has been obtained from the Certified Board of Nippon Medical University according to Clinical Trials ACT.

This trial is registered with UMIN in Japan [clinical trial ID: 000031424] and ClinicalTrials.gov [ID: NCT03777631]. The study design is summarized in Fig. 1.

Patient population

The study patients must satisfy all of the defined inclusion criteria and none of the exclusion criteria described in Table 1. All participants must provide written informed consent following a detailed explanation of the purpose of the study and any risks involved.

Treatment and randomization

Standard medical therapy group

Standard treatment involves oral anticoagulation therapy using the selective Xa inhibitor edoxaban. If required, antiarrhythmic drugs will be allowed for individual patients under the supervision of a well-trained cardiologist.

Cardiac ablation group

CA will be performed within 1–6 months of the ischemic stroke. CA is based on pulmonary vein isolation, with atrial ablation as required.

Randomization into the above treatment groups will be performed using a computer-generated list which will be balanced to take into consideration the $CHADS_2$ score defining the risk of ischemic stroke (<4 or ≥ 4), and the type of AF (paroxysmal AF/other forms of AF) in patients with NVAF.

Study discontinuation

According to worldwide reports of CA [12,13], the incidence of serious adverse events (defined in Table 2) related to CA is

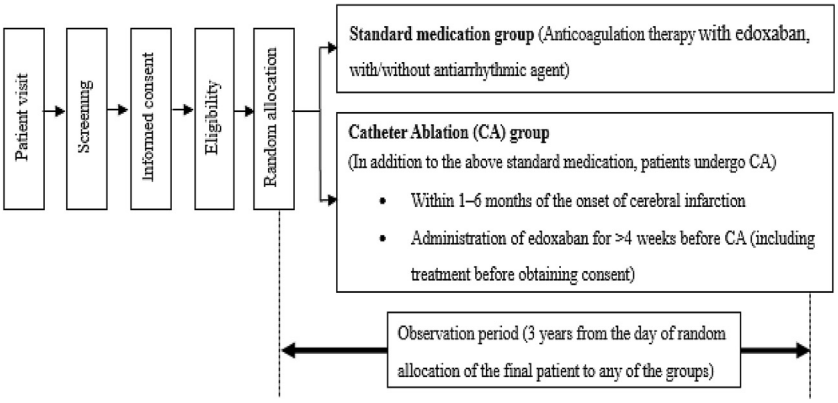

Fig. 1. STroke secondary prevention with catheter ABLation and EDoxaban (STABLED) clinical trial: study design.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria:
Age ≥20 and <80 years at time of giving informed consent
Nonvalvular atrial fibrillation
History of ischemic stroke in previous 6 months
Current or planned treatment with edoxaban
Modified Rankin Scale (mRS) ≤3
Exclusion criteria:
Symptomatic paroxysmal atrial fibrillation resistant to anti-arrhythmic drugs
Presence of left atrial thrombus and/or left atrial appendage on transthoracic echocardiography, computed tomography, or magnetic resonance imaging
Unable to take anticoagulation therapy for any reason, including tendency to bleed or considered at high risk for bleeding from anticoagulation therapy
Presence of severe renal disorder (estimated creatinine clearance <30 mL/min by Cockroft–Gault equation)
Previous catheter ablation or surgical intervention for atrial fibrillation
History of treatment with a left atrial appendage closure device
Left atrial diameter ≥55 mm on transthoracic echocardiography
Ejection fraction ≤35% on transthoracic echocardiography
Persistent atrial fibrillation for ≥10 years
Pregnant or possibility of pregnancy
Unlikely to complete the study, such as due to progressive malignant tumor
Participating or planning to participate in another interventional clinical trial
Unwilling to participate
Judged as incompatible for the study by the investigators

Table 2
Serious adverse events associated with catheter ablation.

Periprocedural death
Cardiac tamponade
Pneumothorax and/or hemothorax
Anemia requiring transfusion
Septicemia/abscess formation/infectious endocarditis
Permanent phrenic nerve paralysis
Pseudoaneurysm and arteriovenous fistula of puncture
Atrial esophageal fistula
Cerebral infarction
Pulmonary venous stenosis required for treatment

approximately 4.5%. The incidence of ischemic stroke associated with general CA is approximately 1% [12]. Thus, the study will be stopped if the incidence of any of these adverse events exceeds the upper limit of the 95% confidence interval after 50 patients have undergone CA. For 50 patients these limits are: serious adverse event 10.25% (>7 patients) and cerebral infarction 3.76% (>3 patients).

Endpoints

Primary outcome

Composite of recurrence of ischemic stroke, systemic embolism, all-cause death, and hospitalization for heart failure over a period of up to 5 years.

Secondary outcomes

- Recurrence of ischemic stroke
- Systemic embolism
- All-cause death
- Cardiovascular death
- Hospitalization for heart failure
- Any bleeding
- Onset of intracranial hemorrhage
- Composite events (all-cause death, onset of stroke, systemic embolism, hospitalization for heart failure, and serious adverse event caused by CA).
- The rate of and related factors to discontinuation of edoxaban
- Recurrence of cerebral infarction in patients with or without discontinuation of edoxaban

Safety outcomes

- Serious adverse events related to CA maneuver
- All adverse events not related to CA maneuver
- Drug reaction to edoxaban

All the above outcomes will be adjudicated by a blinded, independent event adjudication committee.

Data management and monitoring

Data management will be performed using a patient registration system, data entry, patient report forms, and data fixation. Monitoring will assist in confirming the integrity, accuracy, and consistency of the content described in the source material and patient report forms.

Sample size

The rate of occurrence of primary outcomes in the control group is estimated to be 13%/year [14–16]. Assuming CA reduces the primary outcome by 50% [15], when the α error is set to 0.05 and the detection rate is set to 0.8, the required number of patients at 5 years is calculated to be 106 patients in each group, for a total of 212 patients. Assuming a dropout rate of 10%, 250 patients (125 patients in each group) has been set.

Statistical analyses

The details of the statistical analysis plan are shown in the supplementary file "Statistical Analysis Plan". The primary analysis will use the intention-to-treat principle. Serious protocol and ICH-GCP violation and no data after randomization will be excluded from the analysis set. Outcomes are evaluated for events after the day on which edoxaban was continued for 28 days, including treatment before acquisition of informed consent.

For analysis of primary outcomes, the *p*-value will be calculated and examined using the log-rank test with Kaplan–Meier curves for each study group for the first event. A further analysis will be performed based on multivariate Cox regression model. The multivariate analysis model includes the covariates, the allocation factor $CHADS_2$ score, and the type of AF.

For analysis of secondary outcomes, the *p*-value will be calculated and examined using the log-rank test with Kaplan–Meier curves for complex serious adverse events and all bleeding adverse events. In addition, the *p*-value will be calculated and examined using the chi-square test for the percentage of patients with a modified Rankin Scale (mRS) 0–2 and in New York Heart Association (NYHA) Class I for adverse events related to CA, mRS score at the end of follow-up, and NYHA classification at the end of follow-up.

For analysis of safety outcomes, drug reactions to CA and the incidence rate of drug reactions to edoxaban will be calculated together with confidence intervals.

In other statistical analyses, unless otherwise noted all tests are two-tailed, and a *p*-value <0.05 is considered statistically significant. The confidence interval is a two-side confidence interval, and the confidence coefficient is 95%. Missing data will not be supplemented with estimated or calculated values.

Study organization and funding

The organization of the STABLED clinical trial is shown in the supplementary file "Study Organization". The authors will disclose receipt of the following financial support for the study, authorship, and/or publication of this article: the project is supported by Daiichi Sankyo CO., LTD. The study was designed by the steering

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Discussion

CA is a frequently performed procedure to maintain sinus rhythm in AF patients worldwide. For patients with NVAF, CA is performed mainly for symptom relief, and not for reducing the risk of systemic embolism associated with NVAF [17,18]. Patients with NVAF and recent stroke are at high risk for thromboembolism, and CA can potentially reduce the risk of recurrent thromboembolism. In contrast, patients who have had a recent stroke, compared with those who have not, may be at higher risk for adverse events if they undergo CA. No prospective randomized controlled trial to date has focused on this population. The STABLED clinical trial should help clarify the safety of CA for patients who have suffered a recent stroke, and also the efficacy of the procedure by recording not only stroke recurrence but also long-term mortality (up to 5-year follow-up period). The STABLED study will provide evidence for optimal management of patients with NVAF and stroke. In particular, it should provide answers to the question of whether or not CA is effective and safe for patients with recent stroke since non-severe ischemic stroke is one of the indications for CA in NVAF patients, and currently there is no evidence concerning the use of CA in NVAF patients with a recent stroke.

Disclosures

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.06.002.

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