Aug 7th, 2023

Cover page:

To Whom It May Concern,

Please find the Study Protocol and Statistical Analysis Plan of the study “Risk of Stroke and Silent Cerebrovascular Thromboembolism After Cardioversion of Atrial Fibrillation (AFTER-CV)”

(Clinicaltrials.gov Trial registration number: NCT01924065)

Study Protocol

This is a double-blind randomized parallel assignment phase 3 interventional study. Patients with persistent AF with a duration of ≥48hours undergoing elective electrical cardioversion (CV) will be randomized to TEE-guided versus anticoagulation-guided groups.

In the anticoagulation group, the patients are planned to receive warfarin for at least 3 weeks with an INR value between 2.0-3.0. Those who were unable to use or have contraindications to warfarin will receive novel oral anticoagulants (NOACs) at the recommended dose instead of warfarin for at least 3 weeks. If left atrial thrombus is detected by TEE, no CV will be performed. Other patients in the both groups will undergo electrical CV. After the CV, all the patients will be given warfarin or NOACs for at least 4 weeks and the decision to continue anticoagulant after this period was made based on patients'CHA2DS2-Vasc-score. Patients with a score of ≥1 in men and ≥2 in women will take anticoagulation. All the patients will undergo cranial MRI before and 1 week after CV.

Inclusion criteria includes patients with the age of more than 18 years who are planned to undergo electrical CV without anticoagulation use within 48 hours of randomization.

Exclusion Criteria includes urgent CV, patients who have non-MRI compatible implanted pace-makers or other metal devices, claustrophobia, haematological disorders disabling patients to receive anticoagulant agents, AF secondary to temporary causes, serious rheumatic heart valve disease, hyperthyroidism, history of malignancy, left atrium diameter > 55 mm and ejection fraction < 0.25.

Cardioversion

CV will be performed in the fasting state with sedation. R wave-synchronized biphasic direct-current shocks will be delivered in all the patients with the step-up protocol of 100, and 200 J with anterolateral approach. Successful cardioversion was defined as the presence of sinus rhythm lasting≥1 minute after the shock.

MRI

All the patients will undergo diffusion brain MRI before and 1 week after the CV to detect silent cerebral thromboembolic events.

Follow-up

All the patients will be seen at the first week, first month and then every 3-month thereafter, and at any time the patient experienced any symptoms for 2 years. Complete physical exam including neurological exam will be performed in all the cases on the follow-up. Clinical thromboembolic events and bleeding events will be recorded.

Outcome Measures

Efficacy outcome measures: Clinical thromboembolic events including ischemic stroke/transient ischemic attack (TIA), other thromboembolic events or death during 2 years follow-up or acute silent cerebral thromboemboli detected by diffusion MRI at 1 week post-CV.

Safety outcome measures All the bleeding events will be recorded.

Combined outcome measures: Clinical efficacy events or major bleeding during 2 years' follow-up or silent cerebral thromboembolism detected by MRI.

Statistical analysis plan

The significance levels of the tests will be accepted as the P-value of <0.05. Categorical variables will be presented as percentages and will be compared with Chisquare test. Continuous variables will be expressed as mean ± SD. Normality test will be used to test the distribution of continuous variables and variables with normal distribution will be compared with Student t-test and those without normal distribution will be compared with Mann-Whitney U test.

Risk factors for safety and efficacy end-points will be identified using logistic regression analysis. Variables with a p value <0.10 in univariate analysis will be entered into multivariate analysis with stepwise backward elimination method.

The Kaplan-Meier method will be used to compare the probability of freedom from clinical combined end points during long-term follow-up. Intention-to-treat analysis will be performed for follow-up findings.