

Predictors of post-alteplase long-term unfavorable outcome in atrial fibrillation patients presented with embolic stroke in the Middle East and North Africa regions, a multi-center, longitudinal study

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Supplementary Material

Inclusion criteria

Our study involved male and female participants aged 18 to 80 years and their first-ever acute embolic ischemic stroke associated with AF and were candidates for thrombolytic therapy; the participants who were users of direct oral anticoagulants (DOAC) ingested the last dose of DOAC 48 hours or more before stroke onset, and their PT was less than 15 seconds, aPTT was less than 40 seconds. In contrast, warfarin users had INR less than 1.7. Our participants received the recommended full dose of alteplase. There was no imaging evidence of intracranial hemorrhage. (1)

Clinical AF was diagnosed if the participant had a minimum of 30 seconds of cardiac rhythm, showing the absence of P waves and irregular RR intervals (when atrioventricular conduction is not impaired) in a conventional 12-lead ECG recording.

(2)

We did not rule out patients who suffered from previous transient ischemic attack (TIA).

Patients who were included in the long-term outcomes analysis completed a two-year follow-up period.

Exclusion criteria

We ruled out participants who did not receive the full thrombolytic agent dose, patients who did not complete the prespecified follow-up period, patients who suffered from an intracranial tumor, and patients who experienced recurrent CNS disorders such as multiple sclerosis, epilepsy, or a head trauma associated with permanent neurological deficit.

We excluded participants who suffered from end-organ failure, myocardial infarction during the preceding six weeks, and patients who experienced malignant tumors.

We ruled out pregnant and lactating participants, venous sinus thrombosis patients, and patients who experienced stroke following cardiac arrest or severe hypotension.

Study procedures

The clinical assessment of our participants included collecting the data concerning patients' baseline criteria, including age, sex, medical history of diabetes mellitus (DM), hyperlipidemia, AF types and treatment, hypertension (HTN), ischemic heart disease (IHD), smoking, previous drug history, and door-to-needle time. We diagnosed acute hypertensive response when the systolic blood pressure (BP) $\geq$ 140 mm Hg or diastolic (BP) $\geq$ 90 mm Hg on two recordings taken 5 minutes apart within 24 hours of stroke symptom onset (3); we recognized diabetes when the fasting plasma glucose level was more than 126 mg/dl or casual plasma glucose was more than 200 mg/dl, or HbA1C was more than 6.5 (4,5). Admission hyperglycemia was identified if the admission blood glucose value was more than 140 mg/dL (6,7). We identified hyperlipidemia when blood cholesterol was more than 200mg/dL, triglycerides were more than 150mg/dL, LDL-cholesterol was more than 100 mg/dL, and/or HDL-cholesterol was less than 40 mg/dL (8). Moreover, we assessed the HAS-BLED score to evaluate the bleeding hazards. (9)

We also evaluated the CHA₂DS₂VASc score (congestive heart failure, hypertension, age $\geq$ 75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–74 years, sex category [female]) to evaluate the risk of recurrent thromboembolic events in our non-valvular AF patients (10)

The therapeutic history during the follow-up period was assessed, and any treatment received by patients regarding their neurological conditions was recorded, such as (antiplatelets, anticoagulants, anti-seizure medications, anti-hypertensive agents, anti-

hyperlipidemic agents, antidepressants, anti-diabetic medications, and antidementia treatment.

We evaluated the rehabilitation programs conducted during the follow-up period. We detected the duration of the program and the number of patients who underwent early rehabilitation, which started within the first three days after stroke onset (11).

We evaluated recurrent stroke during the follow-up period. We defined recurrent symptomatic ischemic stroke, which occurred during the follow-up period, as any ischemic stroke diagnosed by appropriate brain imaging and associated with NIHSS more than five and/or an increase in mRS by 2 points or more in an otherwise fully recovered patient with a previous stroke(12,13).

We assessed the temperature orally on admission and two times per day during hospitalization (Temp Plus II, Ivac, Giessen, Germany) and diagnosed fever if one or more measurements were $\geq 38^{\circ}\text{C}$ (sub-febrile temperature $37.6\text{-}37.9^{\circ}\text{C}$) and feverish patients received one gram of acetaminophen and specific antibiotics according to the results of the urine, blood, stool, and sputum cultures. (14)

Regarding the cardiological evaluation, all of our participants underwent trans-esophageal echocardiography, 24-hour continuous cardiac rhythm monitoring, and a daily 12-lead routine ECG during their stay in the hospital; we identified permanent AF participants when the admission ECG showed AF, and there was no evidence of sinus rhythm in the last six months before the occurrence of ischemic stroke, in addition, we identified paroxysmal AF patients if they AF on ECG on two separate times, at least two weeks apart, in the last six months before the ischemic stroke. (15) Our participants were categorized into paroxysmal AF or sustained AF; sustained AF patients included persistent and permanent AF, as there were many difficulties in diagnosing persistent and permanent AF separately in routine practice. (16) We also diagnosed heart failure

following the left ventricular ejection fraction (LVEF) detected during echocardiography and categorized heart failure into HF with preserved LVEF (HFpEF) with normal LVEF [typically considered as $\geq 50\%$], HF with reduced LVEF (HFrEF) with LVEF 40% or less, HF with mid-range EF (HFmrEF) with LVEF in the range of 40–49%. (17)

We established the diagnosis of ischemic stroke via history taking, precise clinical examination, and brain imaging, including CT of the brain and CT angiography (CTA) of the brain and neck vessels or MRA brain and neck vessels time of flight (TOF) if CTA was contraindicated before receiving thrombolytic agents.

After receiving the thrombolytic agents, all participants underwent an MRI brain on a 1.5 T (Siemens Essenza) MR system, stroke protocol: T1W, T2W, fluid attenuation inversion recovery imaging (FLAIR), diffusion-weighted imaging (DWI), T2 Echo Gradient, moreover, all of our participants underwent CT brain 24-36 hours after thrombolysis to evaluate any hemorrhagic transformation. (18). The diagnosis of symptomatic hemorrhagic transformation was established if the participant's NIHSS score was elevated by four points or more. (6)

The diagnosis of posterior-circulation stroke (PCS) stroke was established if the occlusion affected basilar, posterior cerebral, or vertebral arteries. The diagnosis of anterior-circulation stroke (ACS) was established if the occlusion affected the internal carotid, middle, or anterior cerebral arteries. (19)

All of our participants received 0.9 mg/kg of alteplase with a maximum dose of 90 mg intravenously within 4.5 hours of stroke onset. Our participants were transferred to our stroke units to complete their treatment. (1)

We followed up with our participants for two years via telephone call once weekly and an interview in our outpatient clinic once every three months. Neurology specialists conducted the telephone calls and the interview. If any patient has clinical deterioration or recurrent stroke manifestations, then they come to our hospital to be assessed via clinical and investigation tools to evaluate their condition .

The mRS and NIHSS used in the trial are free scales that require no formal training or permission and can be used by any neurologist.

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