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Ticagrelor Plus Aspirin vs Clopidogrel Plus Aspirin In Mild Non-cardioembolic Ischemic Stroke: A Protocol Of a Randomized, Controlled, Active Comparator Arm, Outcome Assessor Blind, Feasibility Study

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Ticagrelor plus aspirin vs clopidogrel plus aspirin in mild non-cardioembolic ischemic stroke: A protocol of a randomized, controlled, active comparator arm, outcome assessor blind, feasibility study

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Abstract

Background & Objectives: The risk of recurrence after a transient ischemic attack (TIA) or minor stroke is high especially within three months after first event. The aim of study is assessing the efficacy of ticagrelor plus aspirin in reduction of mild non-cardioembolic ischemic stroke or high risk TIA recurrence during first 3 months. *Methods:* This is a randomized, controlled, active comparator arm, outcome assessor blind, parallel group, feasibility study design on 90 patients with diagnosis of non-cardioembolic minor ischemic stroke or high risk TIA admitted in Bou-Ali Sina Hospital, Sari, Iran. After meeting all inclusion and exclusion criteria, patients will be randomized to ticagrelor 90 mg BID plus aspirin (ASA) 80 mg daily or clopidogrel 75 mg daily plus ASA 80 mg daily (1:1 ratio) until 21 days and then ASA 80 mg daily. Participants will be visited at month one and three. Any adverse events, serious side effects and outcome events will be recorded. The primary outcome is defined as ischemic stroke recurrence.
Conclusion: Ticagrelor plus ASA is expected to be effective for prevention of recurrence in mild non-cardioembolic stroke and high risk TIA.
Trial Registration: ClinicalTrials.gov: NCT04738097

Keywords: Minor stroke; mild stroke; non-cardioembolic; TIA; dual antiplatelet therapy; ticagrelor; clopidogrel; recurrence

INTRODUCTION

Stroke is a leading cause of mortality and disability worldwide. Initial manifestations of acute cerebral ischemia, such as ischemic stroke and transient ischemic attack (TIA), are often followed by recurrent vascular events, including recurrent stroke.[1,2] The risk of recurrence after a TIA or minor stroke is high especially within three months after the first event.[3] Of utmost importance, early secondary stroke prevention modalities have shown to mitigate up to 80% in the risk of stroke after a TIA.[4] The role of aspirin (ASA) in preventing recurrence of stroke is well established[5,6]; yet, several advances have recently been made in pharmacological preventative strategies for first and recurrent strokes.[7] There has been growing evidence that dual antiplatelet therapy (DAPT) may work better than using a single antiplatelet agent. Given together, different agents with different modes of action and variable onset of action may work synergistically, thus inhibiting platelets' aggregation more effectively and with a faster onset of action.[8] Now, DAPT has been widely prescribed for secondary stroke prevention since the publication of clopidogrel with aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) and Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT) trials. Both trials showed the benefit of short-term aspirin plus clopidogrel in the prevention of stroke in patients with a minor stroke or high-risk TIA.[9-11]

The challenge lies in the ineffectiveness of clopidogrel in patients who are CYP2C19

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carriers.[9] Clopidogrel is a prodrug that requires activation by the cytochrome P450 enzyme CYP2C19. Common genetic variation in the CYP2C19 gene, resulting in reduced CYP2C19 activity, has been associated with poorer clinical outcomes for a range of conditions when treated with clopidogrel.[12,13] In fact, several studies investigating the clopidogrel resistance report a prevalence of 15.9% to 49.5%, especially in the Asian ethnicity, indicating a huge population-based variation.[14,15]

Notwithstanding, ticagrelor is a reversible P2Y12 receptor antagonist, which, unlike clopidogrel, does not require conversion from prodrug to active drug in the liver.[1] Ticagrelor was compared directly with aspirin in the SOCRATES trial and showed a strong trend toward lower stroke rates in patients assigned to ticagrelor in the acute setting.[16]

The Platelet Reactivity in Acute Non-disabling Cerebrovascular Events study (PRINCE) result revealed fewer recurrent stroke and composite events in patients treated with ticagrelor plus aspirin than in those treated with clopidogrel plus aspirin. Nevertheless, the authors suggested that the results would need to be replicated, because their study provided a low power.[17]

The rationale of Ticagrelor Plus Aspirin versus Clopidogrel Plus Aspirin in Mild Non-cardioembolic Ischemic Stroke (TACAMINIS) is to evaluate the effects of early DAPT with ticagrelor plus aspirin on prevention of recurrence in mild non-cardioembolic and high risk TIA in Iranian population.

METHODS

Participants

Participants recruitment was began in August 2021. Patients with the diagnosis of ischemic stroke admitted to Bou-Ali Sina Hospital, Sari, Iran were participated in this study if they signed inform consent. Inclusion criteria were: age>40 years; recent ischemic stroke within 24 hours diagnosed by brain CT scan or MRI; mild stroke defined as NIHSS ≤8 when there is no evidence of large infarct in brain imaging or high risk TIA with ABCD2 >4; no cardioembolic source such as low ejection/fraction, mitral valve stenosis, atrial fibrillation, and left atrium enlargement; no specific etiology such as dissection and vasculitis, and no carotid stenosis >50% ipsilateral to the stroke.

Exclusion criteria were: history of hypersensitivity to, or any contraindication for the consumptive drug; any indication for anticoagulant therapy; acute phase treatment with intravenous thrombolysis or thrombectomy; history of intracranial hemorrhage or known coagulopathy; history of gastrointestinal bleeding in the past 6 months; being a candidate for endarterectomy; and active hemorrhagic diathesis during randomization.

Study design

The TACAMINIS is a prospective, randomized, controlled, parallel, active comparator arm, outcome assessor blind, feasibility study (Figure 1). It will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement. The study protocol has been approved by research ethics committees of Mazandaran University of Medical Sciences (approval ID: IR.MAZUMS.REC.1400.304- approval date: 2021-06-23).

The clinical trial is registered with the clinicaltrials.gov web site (registration number: NCT04738097). All participants will sign the written informed consent prior to randomization according to the Declaration of Helsinki.

Randomization and blinding

Participants will be allocated consecutively and randomized to intervention or comparator groups by using 4 block randomization method in a 1:1 ratio and patients list encoded. The codes will be written on the envelopes and the group type (intervention or comparator) will be placed inside the envelope. The envelopes are stacked in order. At the time of enrollment of each patient, the upper envelope will be removed, and based on the group type inside, it is determined which group it belongs to as the intervention or comparator. This study is designed as outcome assessor blind, so the researcher who assesses the patients' outcome will be blinded.

Assessments and outcome measures

Demographic information, risk factors including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, and previous stroke or TIA, as well as the clinical data including baseline NIH Stroke Scale (NIHSS) score, Modified Ranking Scale (MRS) score, and the stroke laterality and territory involvement will be recorded on the case report form. All patients will undergo

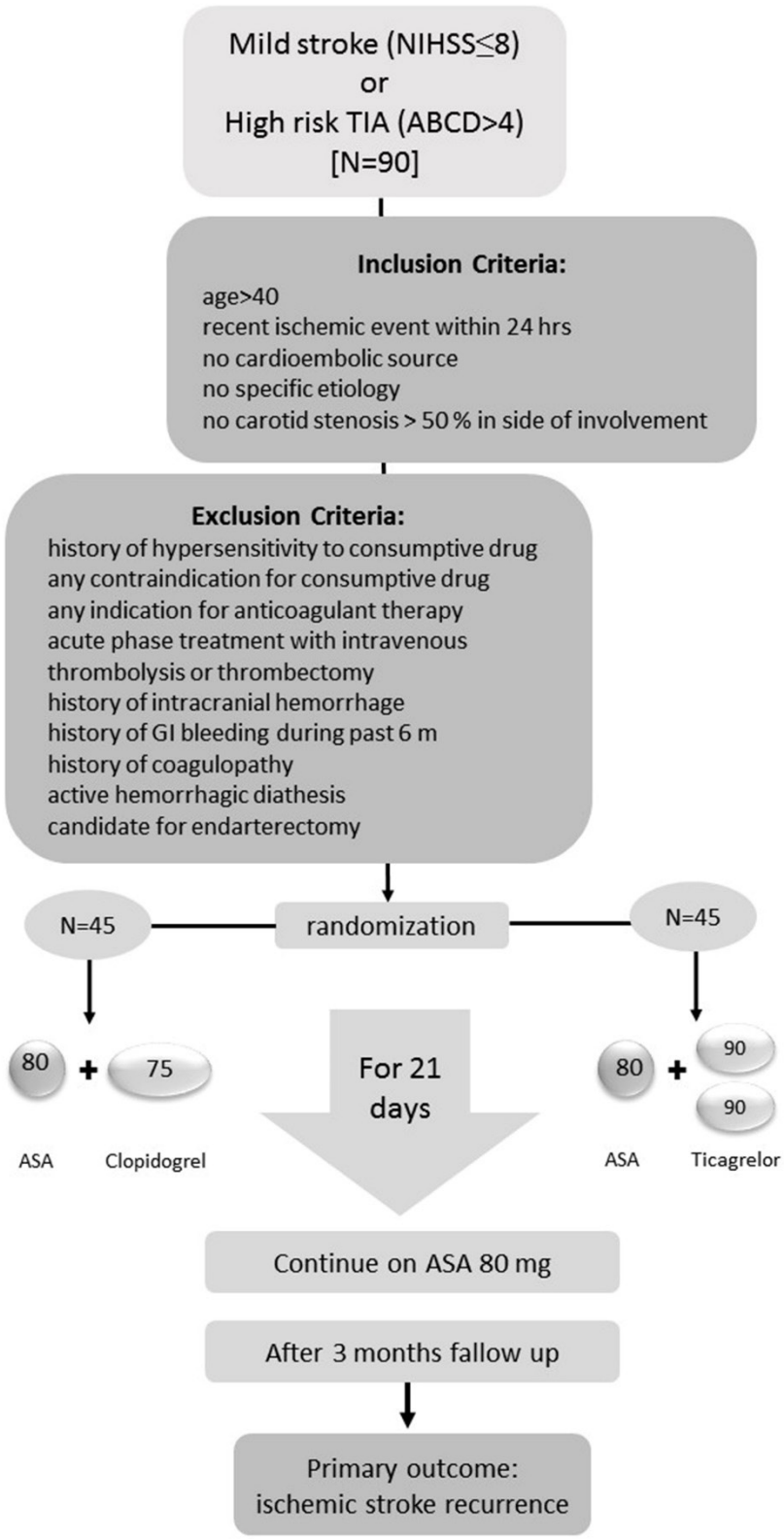

Figure 1. Study design

brain imaging (CT or MRI), along with imaging of extracranial and intracranial arteries (doppler ultrasound or MRA), 12-lead electrocardiogram (ECG), transthoracic echocardiography, and routine laboratory tests. Paraclinical findings will be registered as well. The efficacy and safety end points of the study are considered as stroke recurrence and/or cardiovascular event, and major bleeding according to STIH criteria[18], respectively. Primary outcome is ischemic stroke recurrence during the first 3 months after the first event documented by a new lesion on brain CT or MRI. Secondary outcomes are major hemorrhagic events, stroke recurrence during first 30 days and any cardiovascular event during first 3 months.

Intervention

All patients will receive standard treatment of acute ischemic stroke during hospital admission. Patients in the comparator group will be treated with ASA 325 mg and clopidogrel 300 mg stat, followed by ASA 80 mg and clopidogrel 75 mg daily for 21 days. Intervention group patients will be treated with ASA 325 mg and ticagrelor 180 mg stat, and ASA 80 mg daily and ticagrelor 90 mg BID for 21 days thereafter. Consequently, only ASA 80 mg daily will be continued for all patients after day 21. The study will be continued until all patients are recruited whereas the mean follow-up for each patient is expected to be 90 days. Participants will be monitored by phone contact every 2 weeks along with in-person visits at month 1 and 3. In each visit session, participants will be assessed by a neurologist for checking medication adherence by pill counting, any adverse effect, vital signs, and occurrence of safety concerns or efficacy outcome events.

Safety profile

When a hemorrhagic event occurs during follow up of the patients, the responsible medication will be stopped and appropriate therapeutic measures will be taken into consideration. In spite of permanent cessation of the medication in case of a major bleeding as the safety end point of the study, resuming the treatment after a temporary discontinuation would be accomplished in non-major bleedings in an appropriate clinical setting.

Sample size calculation

Considering PRINCE study[17] result, minor stroke recurrence rate during the first 3 months with standard treatment is 8.8%. With expected minimal clinically difference of at least 50% reduction in recurrence rate, and α =0.05 and power 80%, G-power software calculated 998 participants. Due to the high cost of study and small recruiting center, as well as the TACAMINIS design as a pilot study with 9% requirement of the total sample size[19], 90 participants (45 in each group) were finalized.

Statistical analysis

The primary outcome analyses will be based on per-protocol population. The patients on ASA plus ticagrelor will be compared with the ASA plus clopidogrel 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

Studies have repeatedly shown that DAPT with combination of aspirin and P2Y12 platelet receptor antagonist can reduce the risk of acute thrombotic events and ischemic events recurrence alike.[17] Currently, ASA plus clopidogrel is the most recommendation of many guidelines for secondary prevention in minor stroke and high-risk TIA.[20] However, the unpredictable clopidogrel efficacy of the 5%-55% non-responders limits its use[21], while this rate is trivial in patients treated with prasugrel or ticagrelor.[22]

There is no comprehensive information about resistance rate to clopidogrel in Iranian community. Only in one study on patients after coronary angioplasty, 24.76% resistance to clopidogrel was reported by using light transmission aggregometry in Iranian population.[23]

Ticagrelor, as a potential alternative of clopidogrel for DAPT, has been tested in many studies especially in the field of cardiovascular disorders; yet, there are no head-to-head comparisons after stroke or TIA.[24] Despite comparing ticagrelor and ASA with ASA alone in acute ischemic stroke or TIA (THALES) trial that revealed participants in the ticagrelor plus ASA group had fewer ischemic strokes than those on ASA alone (HR 0.83; 95% CI 0.71–0.96; p=0.02), no comparison has been done with clopidogrel.[25]

In a meta-analysis comparing the effect of clopidogrel and ticagrelor on the cardiovascular outcome of patients with diabetes mellitus (DM) type 2 and acute coronary syndromes, pooled result of 7 studies showed that ticagrelor was associated with a significantly lower risk of major

adverse cardiac events and mortality. However, the risk of minor bleeding was significantly higher with ticagrelor in comparison to clopidogrel in these patients.[26] In another trial on Mediterranean DM patients with coronary syndromes, ticagrelor yielded a more potent platelet inhibition than clopidogrel.[27]

Recently, the CHANCE-2 trial assessed the effects of ticagrelor plus ASA versus clopidogrel plus ASA in Chinese CYP2C19 loss-of-function carrier patients after minor stroke or TIA. At month 3, fewer strokes recurred in the ticagrelor group compared with the clopidogrel group (6.0% vs 7.6%, respectively; HR 0.77; 95% CI 0.64–0.94).[28] Similar to previous studies, minor bleeding was more common in ticagrelor group, but no difference in major bleeding was reported.[28]

Finally, data from the recent studies raise the ponderable question of whether clinicians can substitute clopidogrel by ticagrelor as add-on therapy to aspirin for DAPT in mild stroke and high-risk TIA.[24] Such being the case, conducting a head-to-head comparison trial in an Iranian population that can compare the effectiveness of aspirin plus clopidogrel versus aspirin plus ticagrelor seems to be warranted.

In conclusion, the results of TACAMINIS may provide important advances in planning for DAPT in Iranian population to prevent recurrence of mild non-cardioembolic stroke and high-risk TIA.

DISCLOSURE

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