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

Nasim Tabrizi, Razieh Daz, Athena Sharifi-Razavi

Neurology Department, Clinical Research Development Unit of Bu-Ali Sina Hospital, Mazandaran University of medical Sciences, Sari, Iran

Abstract

Background: The risk of recurrence after a transient ischemic attack (TIA) or minor stroke is high especially within three months after the first event. The aim of the present study was to assess the efficacy of ticagrelor plus aspirin in reduction of mild non-cardioembolic ischemic stroke or high-risk TIA recurrence during the first 3 months. *Methods:* This was a randomized, controlled, active comparator arm, outcome assessor blind, parallel group, study designed on 90 patients with diagnosis of non-cardioembolic mild ischemic stroke or high-risk TIA admitted in Bu-Ali Sina Hospital, Sari, Iran. After meeting all inclusion and exclusion criteria, patients were randomly assigned 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 were visited at month one and three. Any adverse events, serious side effects and outcome events were recorded. The primary outcome was defined as ischemic stroke recurrence. *Results:* Ninety-four patients were recruited into this study (47 in ticagrelor and 47 in clopidogrel group). Stroke recurred in 2 patients in the clopidogrel group and no recurrence noted in the ticagrelor group (OR: 0.18; 95% CI = 0.008–3.932, P=0.27). No major hemorrhagic event occurred in either group.
Conclusion: Ticagrelor plus aspirin and clopidogrel plus aspirin showed similar efficacy and safety in preventing recurrence of mild non-cardioembolic stroke and high-risk TIA. However, uncertainties remain due to the small sample size, and larger trials are needed.

Keywords: Mild stroke, non-cardioembolic, TIA, dual antiplatelet therapy, ticagrelor

INTRODUCTION

Globally, stroke continued to be the third leading cause for disability-adjusted life years and the second most prevalent cause for mortality.[1-3] Individuals who have experienced a transient ischemic attack (TIA) or minor ischemic stroke are at an increased risk of experiencing another stroke. Stroke recurrence rates in the next three months vary from 10 to 20 percent.[4-6]

Nowadays, the most important and cost-effective treatment to prevent experiencing another stroke in individuals with a history of non-cardioembolic minor stroke and TIA is dual antiplatelet therapy which consists of one P2Y12 inhibitor added to aspirin.[7-11]

Nevertheless, there is a continuous potential for bleeding linked to the use of these agents, so choosing antiplatelet therapy carefully is essential for successful stroke prevention.[12] Clopidogrel is a platelet inhibitor that binds to the P2Y12ADP receptors on platelets, irreversibly. However, clopidogrel is a prodrug that is absorbed by intestinal cells[13-15] and requires a two-step biotransformation to generate an active metabolite by an enzymatic member of the cytochrome P450, CYP2C19.

Individuals with loss of function (LOF) mutations do not benefit from the inhibitory platelet function of clopidogrel as patients without LOF mutations do because they are less able to produce the active metabolite.[16-19]

Address correspondence to: Athena Sharifi-Razavi, Bu Ali Sina Hospital, Pasdaran Boulevard, Sari, Iran. email: Athena.sharifi@yahoo.com

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In such cases, alternative antiplatelet drugs, that do not require CYP2C19 enzyme bioactivation in the liver, may be taken into consideration.[20] Ticagrelor is a powerful direct-acting agent that binds reversibly to and blocks the P2Y12 receptors for adenosine diphosphate on platelets and does not require hepatic activation.[21-25] Furthermore, ticagrelor is administered twice a day and enables a more stable and uniform suppression of platelet function for the entire 24-hour period.[26]

The prevalence of clopidogrel resistance varies from 17 to 25% within certain populations. According to reports, clopidogrel resistance in Asian communities has not been thoroughly investigated up to this point.[27,28] Evidence from Iranian population is especially sparse, with only two studies showing a mean of 20.5% for clopidogrel resistance inside the studied population.[29,30] In light of this lack of clarity, we set out to compare the efficacy and safety of ticagrelor and aspirin versus clopidogrel and aspirin in mild non-cardioembolic ischemic stroke (TACAMINIS) and high-risk TIA on prevention of recurrence in Iranian population.

METHODS

The design and rationale of TACAMINIS has previously been published.[31] In brief, it was a prospective, randomized, parallel- group, outcome assessor blind, placebo- controlled feasibility study to evaluate the safety and efficacy of dual antiplatelet therapy, comparing aspirin plus ticagrelor versus aspirin plus clopidogrel in cases of mild non-cardioembolic stroke or high-risk TIA in terms of preventing ischemic stroke recurrence. Each patient provided written informed consent as part of the Helsinki Declaration's guidelines for conducting research. Its protocol has been authorized via the institutional overview board and ethics committee board of Mazandaran University of Medical Sciences (approval number: IR.MAZUMS.REC. 1400.304- approval date: 2021-06-23.) and registered in Clinicaltrials.gov (NCT 04738097).

Study population

Patients hospitalized in Bu-Ali Sina Hospital, Sari, Iran with the diagnosis of ischemic stroke were participated in this study (August 2021-Septembre 2023) after signing the inform consent. The following are the definition of the inclusion criteria: age greater than 40 years; diagnosis of ischemic stroke based on brain Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) within the last 24 hours; mild stroke (National Institutes of Health Stroke Scale (NIHSS) score ≤8) in the absence of imaging evidence indicating a large infarct or the presence of high-risk TIA (ABCD2 >4); absence of a cardioembolic source including conditions like atrial fibrillation, enlarged left atrium, stenotic mitral valve, and diminished ejection fraction; no specific identifiable cause such as vasculitis, dissection, and particularly greater than 50% stenosis of the carotid artery ipsilateral to the stroke. The following categories were excluded: any contraindication or history of allergic reaction to the medication in question; any necessity to use anticoagulants; intravenous thrombolytic treatment or thrombectomy in acute stroke phase; history of gastrointestinal bleeding in the previous six months; history of intracranial hemorrhage; known coagulopathy or active hemorrhagic diathesis during randomization, and qualifying for endarterectomy.

Randomization, assessment and outcomes

Participants allocated consecutively and randomized to either the intervention or comparator groups. Randomization was performed using a computer-generated random sequence with allocation concealment by sealed opaque envelopes. This study designed to be blind to the outcome assessors, meaning that the neurologist evaluating the patients' outcomes was unaware of the treatment assignments.

Demographic information, risk factors, clinical characteristics including the baseline NIHSS score and the Modified Rankin Score (mRS) were recorded. All patients underwent brain imaging techniques such as CT or MRI, along with the imaging of both extracranial and intracranial arteries using Doppler Ultrasound or MR Angiography (MRA), as well as a 12-lead electrocardiogram (ECG), transthoracic echocardiography (TTE), and ordinary laboratory assessments.

Primary outcome was ischemic stroke recurrence at some stage in the first 3 months following the initial incident, as shown by the presence of a new lesion observed on a brain CT or MRI. Secondary outcomes were significant hemorrhagic events, and any cardiovascular incidents that occurred within the first three months. The study evaluated efficacy and safety secondary endpoints based on the recurrence of

stroke and/or cardiovascular events, and major hemorrhage according to the STIH criteria.[32]

Intervention

All patients were treated with standard stroke protocol of acute ischemic stroke all through their hospital stay. Participants within the comparator group received an initial treatment of aspirin 325 mg and clopidogrel 300 mg, followed by a 21 consecutive daily regimen of aspirin 80 mg and clopidogrel 75 mg. Patients in the intervention group were given aspirin 325 mg and ticagrelor 180 mg as a start dose, followed by aspirin 80 mg daily and ticagrelor 90 mg twice a day for the subsequent 21 days. Consequently, only aspirin 80 mg daily were persevered for all patients following the 21st day of the treatment regimen.

For each patient, a mean follow-up of ninety days was anticipated. In addition to in-person visits at months one and three, participants were observed via phone every two weeks. Every time a participant visited for a consultation, a neurologist would evaluate them for medication adherence using pill counting, complications, and vital signs, alongside the occurrence of any safety issues or efficacy outcome measures.

Sample size calculation and statistical analysis:

Considering PRINCE study 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. TACAMINIS design as a pilot study with 9% requirement of the total sample size, about 90 participants (45 in each group) were finalized.[31]

All statistical analyses were performed with SPSS statistical software, V.20. Every test was conducted as a two-sided analysis, with a p-value of less than 0.05 deemed as statistically significant. A per-protocol analysis was used for the primary outcome analyses; given the feasibility design and small sample size although we acknowledge that intention-to-treat is standard in confirmatory trials.

Throughout the 90-day period of patients' follow-up, differences in effectiveness and safety outcomes were evaluated by a logestic regression model, Odds Ratio (OR) with a 95% Confidence Interval (CI).

RESULTS

Between August 2021 and September 2023, one hundred participants have been enrolled in the study and they were randomized to be placed in one of two groups: the intervention (52 patients) or the comparator (48 patients) group. But, 94 patients (47 in each arm) completed the study and statistical analysis was performed on them. Figure 1 shows the study flowchart.

Adherence to study medication was >90% in both arms, as assessed by pill count.

The participants' mean age was 65.98 ± 9.91 years, while 49 patients were females (52.12%). Both groups demonstrated no statistically significant differences regarding age, gender, drug history, stroke severity, infarct side and involved territory, as shown in Table 1.

During the study, stroke recurrence was noted in 2 patients in the comparator group 8 and 88 days after the first event and no stroke recurred in the intervention group (Table 2). However, two groups did not differ significantly (OR: 0.18; 95% CI = 0.01–3.93, P=0.27). Figure 2 showed mRS distribution between two arms.

No cardiovascular or systemic embolic event occurred in either group. Also, no major bleeding event was recorded in either group. Minor bleeding, including easy bruising and mild epistaxis, occurred in 2 patients from the intervention group. No statistically significant difference has been observed (OR: 2.94; 95% CI= 0.12-73.95, P: 0.51).

In term of other adverse events, dyspnea occurred in 9 patients from 52 (17.30%) in ticagrelor, that in 2 patients led to drug discontinuation, and in 7 other patients, it was mild and resolved after a few days. Adherence rate was 95.74% in ticagrelor and 97.87% in clopidogrel group. No death occurred in either groups.

DISCUSSION

Overall, our study suggests that ticagrelor and clopidogrel have broadly similar efficacy and safety profiles, though the small sample size limits definitive conclusions. Higher bleeding risk with ticagrelor remains a clinical consideration.

The beneficial inclination of ticagrelor versus aspirin was first reported in SOCRATES study while 5.8% and 6.7% of patients in the ticagrelor and in the aspirin group, respectively, experienced an ischemic stroke (HR: 0.87; 95% CI, 0.76 - 1.00; P = 0.046).[33] This study found that the group receiving ticagrelor showed a

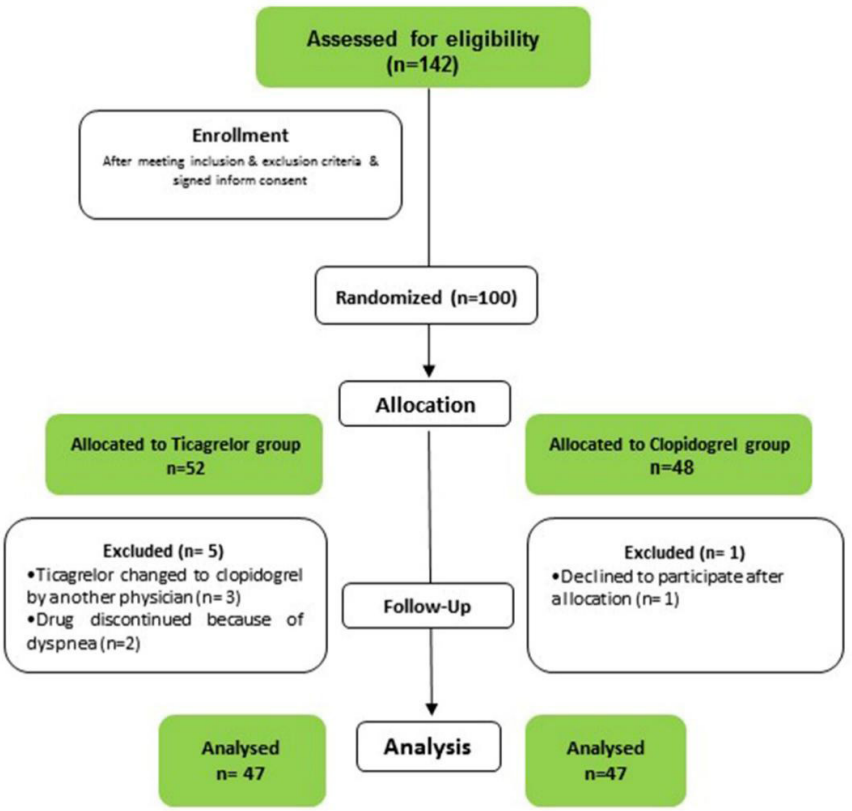

Figure 1. Study flowchart

trend toward greater effectiveness in lowering vascular incidents risk but also higher bleeding rates, in comparison to the group that received aspirin, particularly in the Asian subpopulation.[34]

A current meta-analysis comparing the efficacy and safety of ticagrelor opposed to aspirin and clopidogrel advise that ticagrelor is slightly better than clopidogrel and aspirin in preventing cerebrovascular events, especially ischemic strokes.[35]

Adding ticagrelor to aspirin in the THALES study reduced the RR of stroke or death 17% more compared with the placebo, with a Number-Needed-to-Treat (NNT) of 92 to prevent one stroke or death at one month from the start day.[36] In this study, 5% of patients in the ticagrelor–aspirin group and 6.3 percent of patients in the aspirin group (HR:0.79; 95 % CI, 0.68 - 0.93; P = 0.004) reported having a subsequent ischemic stroke after suffering a non-severe acute non-cardioembolic ischemic stroke (NIHSS score ≤5) or TIA.[37] Furthermore, ticagrelor plus Aspirin produced a clinically significant relative risk (RR) reduction of disabling stroke and death as opposed to aspirin alone.[38]

In the PRINCE study, patients who received ticagrelor and aspirin for minor stroke or TIA had a smaller percentage of excessive platelet reactivity compared to those receiving clopidogrel and aspirin; this difference was primarily seen in patients who carried the CYP2C19 loss-of-function allele. Stroke occurred in 6.3% and 8.8% of patients in the ticagrelor plus aspirin group and clopidogrel plus aspirin group, respectively (HR:0.70; 95% CI 0.40 -1.22; P=0.20). At 90 days, the ticagrelor plus aspirin group's patients with large artery atherosclerosis experienced a lower stroke recurrence (6.0 %) compared to another group (13.1 %) (HR: 0.45; 95 % CI, 0.20 - 0.98; P=0.04).[39,40]

In order to determine whether ticagrelor plus aspirin, as opposed to clopidogrel and aspirin, would reduce the risk of stroke in patients with high-risk TIA or minor ischemic stroke who carry the CYP2C19 loss-of-function allele, the CHANCE-2 study was turned into designed. A new stroke, whether ischemic or hemorrhagic type, occurred in 7.6% of the patients in the

Table 1: Baseline data between the two groups

		Ticagrelor N=47 Mean(SD)/ Number(%)/ Median(IQR)	Clopidogrel N=47 Mean(SD)/ Number(%)/ Median(IQR)	p
Age		65.96 (9.68)	66.02 (10.24)	0.63
Sex: female		27 (57.45)	22 (46.80)	0.48
Risk factors	Diabetes Mellitus	19 (40.43)	16 (34.04)	0.35
	Hypertention	34 (72.34)	32 (68.08)	0.48
	Hyperlipidemia	12 (25.53)	15 (31.91)	0.11
	Coronary artery disease	16 (34.04)	12 (25.53)	0.06
	Previous stroke or TIA	7 (14.89)	5 (10.63)	0.11
Drug history	Antiplatelet	14 (29.79)	12 (25.53)	0.27
Carotid artery stenosis (less than 50%)		31 (65.96)	33 (70.21)	0.55
Stroke severity	Premorbid mRS	0 (0,0)	0 (0,0)	0.15
	Discharge mRS	2 (1,3)	2 (1.5,3)	0.59
	Month3 mRS	0 (0,1)	0 (0,1)	1.00
	NIHSS discharge	4 (3,5)	4 (2.5,5)	0.06
	NIHSS month 3	0 (1,2)	0 (0,1.5)	0.27
Stroke characteristics	TIA	9 (19.15)	10 (21.28)	0.61
	Posterior territory involvement	20 (42.55)	17 (45.95)	0.81
	Left side involvement	29 (61.70)	24 (51.06)	0.13

clopidogrel plus aspirin group but only in 6.0% of patients in the ticagrelor plus aspirin group during the 90-day period (HR, 0.77; 95% CI, 0.64 to 0.94; P = 0.008).[41] Furthermore, this preventive effect persisted for up to 12 months of follow-up.[42]

A secondary analysis of the CHANCE-2 study advised that the main clinical advantage of combined antiplatelet treatment with ticagrelor plus aspirin compared to clopidogrel plus aspirin may be apparent within the first week, with further slight benefit accruing in the second and third weeks.[43] In another secondary analysis, obese patients obtained greater clinical benefits from the ticagrelor plus aspirin treatment in comparison with those without obesity.[44] Also, the post hoc analysis of the CHANCE-2 study reported that CYP2C19 LOF carriers with minor stroke or TIA who were at lower chance of recurrent stroke[45] and patients without intracranial artery stenosis benefited more from ticagrelor and aspirin than from clopidogrel and aspirin.[46]

Additionally, the result of a recent meta-analysis showed the rate of stroke recurrence did not show a significant difference between the ticagrelor plus aspirin and the clopidogrel plus aspirin groups (OR:1.16; 95% CI, 0.93–1.44).[47]

Table 2: Outcome events between the two groups

Outcome	Ticagrelor N=47	Clopidogrel N=47	Odds Ratio	95% CI	p
Stroke recurrence	0	2	0.18	0.01–3.93	0.27
Minor hemorrhagic event	2	0	2.94	0.12-73.95	0.51

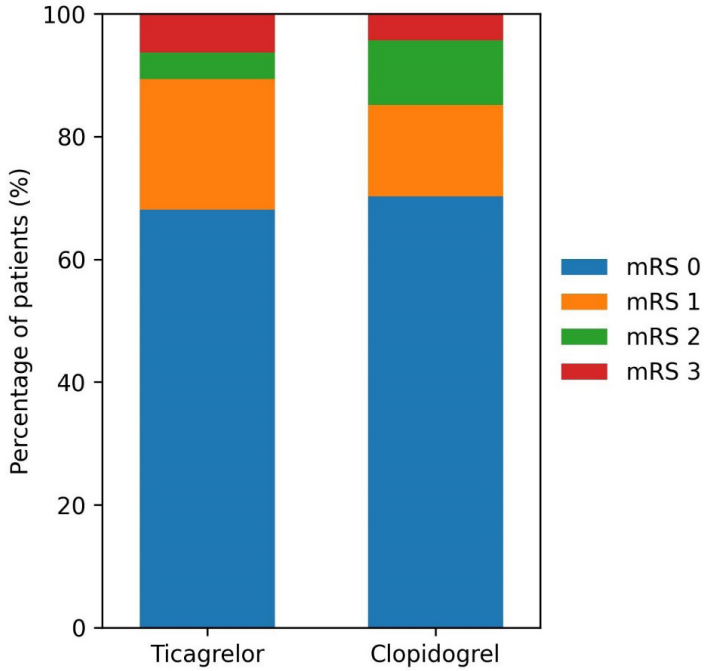

Figure 2. Distribution of modified Rankin Scale (mRS) at 3 months between the two groups.

However, subgroup analysis in Asian and particularly Chinese participants confirmed that ticagrelor was found to lower the ischemic stroke recurrence risk (OR: 0.77; 95% CI, 0.63- 0.92) in comparison to clopidogrel when they were added to aspirin.[47]

In patients older than 80, ticagrelor plus aspirin was unable to change the efficacy or safety outcomes according to another subgroup analysis of the two treatment groups in the CHANCE-2 trial.[48]

In clinical practice, the hemorrhagic risk has been a main concern whilst administering a dual antiplatelet regimen to patients who have experienced an ischemic stroke or TIA.[49] Notwithstanding, previous trials showed short-term combination of aspirin and clopidogrel would not raise the risk of major bleeding in such cases.[50,51]

Whereas, bleeding is the most significant complication of ticagrelor. Owing to differing interpretations of bleeding, the occurrence of ticagrelor-induced bleeding reported in the literature varies widely, ranging from 3% and 32%.[52] The main hemorrhagic events related to ticagrelor encompass epistaxis, subcutaneous hemorrhage, gastrointestinal hemorrhage, and intracranial hemorrhage.[53] In the present study, however, only minor bleeding, including easy bruising and mild epistaxis, occurred in 2 patients (2.35%) in the ticagrelor group.

While we discovered no significant difference between ticagrelor and clopidogrel regarding bleeding-related complications, ticagrelor, as opposed to clopidogrel, is linked to a considerably excessive occurrence of clinically relevant bleeding adverse events when used in conjunction with dual or triple antithrombotic therapy.[53]

The DISPERS trial revealed that ticagrelor was associated with a higher risk of minor bleeding but fewer major bleeding complications when compared to clopidogrel.[54] A meta-analysis was carried out to evaluate the safety and effectiveness of ticagrelor in Asian population with Acute Coronary Syndrome (ACS) in the real-world setting, in comparison to clopidogrel. The results demonstrated that ticagrelor can diminish the likelihood of significant negative cardiac incidents by lowering the risk of stroke, all while not rising the major hemorrhage rates.[55] Moreover, no differences were detected in the major or minor bleeding events between the ticagrelor and clopidogrel groups when they were combined with aspirin (4.8% *v* 3.5%; P=0.42) in the PRINCE study.[39]

In the CHANCE-2 trial, ticagrelor and clopidogrel groups experienced similar rates of moderate to severe bleeding (0.3%); yet, mild hemorrhagic events occurred more commonly in the ticagrelor group (5% vs 2.2%).[41]

In term of other complications, ticagrelor can induce various side effects, such as dyspnea, ventricular pause, gout, renal impairment, and thrombotic thrombocytopenic purpura. Dyspnea is the most common complication related to clinical use of ticagrelor. In most patients, however, it has a tendency to has a mild to moderate intensity and a self-limited course, frequently happens within the initial phases of treatment, last for a few days to weeks, and have no appreciable impact on blood oxygen levels and vital capacity.[56,53] Dyspnea with diverse severity levels can occur in up to 38.6% of patients receiving ticagrelor in various studies. Approximately 6.5% of patients who experience dyspnea would discontinue the medication early.[57]

In the PLATO study, dyspnea has been stated in 13.8% of patients in the ticagrelor group.[58] Mehdizadeh Parizi *et al*. has reported dyspnea rate of 44.3% and discontinuation rate of 2.8% in an Iranian population.[59] In our study, 17.30% of patients suffered from dyspnea and the discontinuation rate was 3.84%.

One of the advantages of this study is that, based on our best knowledge, it is the first study on the effect of ticagrelor in the Iranian population with ischemic stroke. Moreover, we examined dual antiplatelet therapy in patients with higher NIHSS score (<8) in comparison with previous studies, albeit we evaluated the volume of stroke by brain CT and or MRI and excluded the ones prone to hemorrhagic transformation.

The notable limitations of the current trial include its small sample size and brief follow-up period.

In conclusion, this feasibility clinical trial indicates that ticagrelor plus aspirin and clopidogrel plus aspirin may provide similar protection against recurrent mild non-cardioembolic stroke or high-risk TIA. Due to the small sample size and short follow-up, larger randomized controlled trials are warranted to confirm these findings.

This clinical trial enhances our understanding of the comparative efficacy and safety of dual antiplatelet therapy using ticagrelor and aspirin in preventing recurrence of mild non-cardioembolic strokes and high-risk TIAs among the Iranian populace.

Research on antiplatelet therapy for stroke should aim to develop clinical trial level evidence in populations worldwide, just like many other areas of medical investigation. This will contribute to the development of a personalized medicine approach to stroke treatment that will benefit all stroke patients and may also help address racial disparities.

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DISCLOSURE

Ethics: Mazandaran University of Medical Sciences approved this study protocol.

Data availability: Individual participant data are available upon reasonable request from the corresponding author.

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Conflicts of interest: None

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