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ORIGINAL RESEARCH

CILO-CLOP Trial: Cilostazol Versus Clopidogrel in Acute Moderate and Moderate-to-Severe Ischemic Stroke: A Randomized Controlled Multicenter Trial

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ABSTRACT

***Introduction*:** All large studies evaluating the role of cilostazol versus other antiplatelet agents in stroke prevention have been conducted in Asia and included patients with minor stroke or transient ischemic attack (TIA). Ours is the first-ever trial to evaluate the safety and efficacy of cilostazol versus clopidogrel in moderate and moderate-to-severe ischemic stroke in North Africa. Accordingly, in this study we assess the role of cilostazol as an alternative to clopidogrel in Egyptian patients with first-ever non-cardioembolic moderate or moderate-to-severe ischemic stroke.

***Methods*:** A total of 870 patients with moderate and moderate-to-severe acute ischemic stroke (AIS) were randomly assigned to administration of loading and maintenance doses of cilostazol or clopidogrel.

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***Results*:** Of the 870 patients included in our trial, 37 (8.7%) in the cilostazol arm and 59 (13.6%) in the clopidogrel arm experienced a new stroke (HR 0.53; 95% CI, 0.33–0.84; $P=0.007$). Twelve participants (2.8%) in the cilostazol group and 25 patients (5.7%) in the clopidogrel group experienced drug-related hemorrhagic complications (HR 0.25; 95% CI, 0.12–0.53; $P=0.001$). Patients with hypertension who received cilostazol had significantly lower rates of recurrent hemorrhagic and ischemic stroke.
***Conclusion*:** Egyptian patients with non-cardioembolic moderate and moderate-to-severe ischemic stroke who received cilostazol within the first 24 h of symptoms had significantly lower rates of hemorrhagic transformation of brain infarction and peripheral hemorrhagic complications than those who received clopidogrel. Patients with hypertension achieved the greatest benefit from cilostazol, as they experienced a significant reduction in recurrent ischemic and hemorrhagic infarction. There were no significant differences between the two groups regarding the modified Rankin scale (mRS) score after 3 months or in the non-hemorrhagic side effects. Our results were derived from a single-blinded study; a more extensive, double-blinded, multinational study is needed for the results to be generalizable worldwide.
Trial Registration: Retrospectively registered, ClinicalTrials.gov, NCT06242132, 27-01-2024.

Keywords: Cilostazol; Egypt; Clopidogrel; Moderate ischemic stroke; Moderate-to-severe stroke

Key Summary Points

Why carry out this study?

The use of antiplatelet therapy in acute ischemic stroke (AIS) produces better functional outcomes.

All large studies evaluating the role of cilostazol versus other antiplatelet agents in stroke prevention have been conducted in Asia and included patients with minor stroke or transient ischemic attack (TIA).

We aimed to evaluate the efficacy and safety of cilostazol as an alternative to clopidogrel in patients with moderate and moderate-to-severe ischemic stroke to support the tailored use of antiplatelet agents in patients at higher risk for hemorrhagic complications.

What was learned from the study?

Egyptian patients with moderate and moderate-to-severe ischemic stroke who received cilostazol had significantly lower rates of hemorrhagic transformation of brain infarction and peripheral hemorrhagic complications than those who received clopidogrel.

There were no significant differences between the cilostazol and clopidogrel arms regarding the modified Rankin scale (mRS) score after 3 months and the non-hemorrhagic side effects.

INTRODUCTION

Antiplatelet medications are the most important agents for reducing the risk of recurrent stroke, myocardial infarction, and other vascular occlusive syndromes that develop after ischemic stroke [1, 2]. Non-cardioembolic moderate and moderate-to-severe ischemic strokes differ from minor stroke and transient ischemic attack (TIA), as the latter necessitate the use of a single antiplatelet agent as a secondary preventive agent, compared to dual antiplatelet treatment following minor stroke and TIA [3]. Moderate and moderate-to-severe ischemic stroke are also associated with higher rates of poor post-stroke outcome and higher risk of hemorrhagic transformation of brain infarction [4, 5].

When cilostazol was compared with aspirin and ticlopidine, it showed comparable ability to inhibit platelet reactivity and aggregation

to that produced by ticlopidine and aspirin, while also producing fewer hemorrhagic side effects [6, 7]. Although clopidogrel is one of the commonest antiplatelet agents used for secondary prevention of stroke and ischemic heart disease, 20–50% of individuals exhibit clopidogrel resistance or poor response. As a result, other antiplatelet agents are used to prevent ischemic stroke recurrence [8, 9].

All large studies with sufficient power that have evaluated the role of cilostazol in stroke prevention have been conducted in Asia and included patients with acute minor stroke or TIA [10]. Therefore, we aimed to evaluate the efficacy and safety of cilostazol as an alternative to clopidogrel in moderate and moderate-to-severe ischemic stroke to support the tailored use of antiplatelet agents such as cilostazol, which has a lower risk of hemorrhagic complications, especially in patients with large infarction core and high baseline National Institutes of Health Stroke Scale (NIHSS) score, such as those with moderate and moderate-to-severe stroke, which has a higher incidence of hemorrhagic complications [11].

METHODS

Trial Design

Our trial aimed to assess the efficacy and safety of cilostazol in comparison with clopidogrel in Egyptian patients who suffered from a first-ever non-cardioembolic moderate or moderate-to-severe ischemic stroke.

Ethical Approval

Our study was approved by the ethical committee of Kafr El-Sheikh University (reference number KFSIRB200-145). We obtained formal written consent from the patients or their next of kin if the patients were illiterate or critically ill. Our study did not contain any identifiable information regarding our patients.

We assessed all patients who experienced a first-ever moderate or moderate-to-severe ischemic stroke and presented at Kafr El-Sheikh University Hospital, Al Obour Insurance Hospital in Kafr El-Sheikh, or El-Sahel Teaching Hospital in Cairo between 1 October 2022 and 1 October 2024; the last patient joined the trial on 5 September 2024.

Both the cilostazol group and clopidogrel group comprised 435 patients, for a total of 870 patients, with 145 patients recruited for each group from Kafr El-Sheikh University Hospital, Al-Obour Insurance Hospital, and El-Sahel Teaching Hospital.

All the participants underwent randomization on admission and were administered the antiplatelet agents within 24 h after stroke onset. Patients received cilostazol or clopidogrel in a 1:1 ratio according to a computer-based randomization plan with a four-block size.

Our trial was retrospectively registered, as the principal investigator delayed the study's registration until most data acquisition was completed for confidentiality reasons concerning the study methods. Moreover, when the trial was started, we were unfortunately unaware of the policy of the International Committee of Medical Journal Editors (ICMJE), which requires prospective registration of all interventional clinical trials. We registered the trial at ClinicalTrials.gov (identifier no. NCT06242132, 27-01-2024) as soon as we became aware of this policy.

Participants

The trial included male and female patients who had experienced acute first-ever non-cardioembolic moderate or moderate-to-severe ischemic stroke. The study had two parallel groups: group A, which involved 435 patients who received cilostazol, and group B, comprising 435 patients who received clopidogrel.

Eligibility Criteria

Inclusion Criteria

The study included male and female patients, aged 18–75 years, who had experienced acute first-ever non-cardioembolic moderate or moderate-to-severe ischemic stroke. Moderate

stroke was diagnosed when patients had an NIHSS score between 5 and 15, while moderate-to-severe stroke was diagnosed for NIHSS scores from 16 to 20 [12, 13]. All participants were administered antiplatelet therapy during the 24 h after the onset of stroke symptoms. Patients older than 75 years were excluded in order to decrease the probability of atrial fibrillation (AF), which increases with increasing age [14, 15]. Participants who had experienced previous TIA were allowed to be included in our study.

Exclusion Criteria

We did not include any patient who received antiplatelet, anticoagulant, or alteplase agents during the 72 h before randomization to prevent the effects of such treatment from obscuring the evaluation of our treatment safety [3]. In addition, we ruled out patients whose NIHSS score was less than 4 or greater than 20 and patients with neurological diseases associated with recurrent neurological deficits, such as epilepsy, multiple sclerosis, or head trauma followed by neurological deficit.

We excluded patients with cardiovascular disorders in which cilostazol was contraindicated, such as unstable angina, myocardial infarction, and heart failure (defined as ejection fraction < 40% of normal in echocardiography) [16], and patients who had undergone percutaneous coronary intervention within the previous 6 months, as cilostazol has a positive inotropic effect and increases the risk of mortality in patients with heart failure [17].

We also excluded patients who had suffered cardioembolic stroke. Cardioembolic stroke was suspected when the patient experienced conditions associated with a cardiac source of emboli such as mechanical cardiac valves, AF, or patent foramen ovale [18, 19]. Clinical AF was diagnosed when there was at least 30 s of cardiac rhythm demonstrating the absence of P waves and irregular RR intervals in a 12-lead electrocardiogram (ECG) [20].

We excluded patients who were regular users of medications affecting cilostazol metabolism, such as macrolide antibiotics, proton pump inhibitors (e.g., omeprazole), and sertraline [21], and drugs affecting clopidogrel metabolism, such as proton pump inhibitors, statins, and rifampin [22]. We did not include patients who underwent carotid, cerebrovascular, or coronary revascularization during the first week of the trial to avoid clouding of efficacy and safety analysis.

Our study did not include patients who experienced recurrent ischemic stroke detected from their clinical data or magnetic resonance imaging (MRI) brain findings. In addition, we excluded patient who experienced hypersensitivity to cilostazol or clopidogrel and patients who had an international normalization ratio (INR) greater than 1.4, prothrombin time (PT) greater than 18 s, or < 100,000 platelets per microliter.

We did not include patients who experienced organ failure such as renal failure or liver cell failure, those with active malignancies, or those with a history of active peptic ulcer bleeding within the last year. We also excluded pregnant and lactating women, patients with cerebral venous thrombosis, and patients with stroke associated with cardiac arrest.

Interventions

Treatment Dosing

The trial comprised two arms. Arm A consisted of 435 patients who were administered a 200 mg loading dose of cilostazol within 24 h after stroke symptoms, then continued on 100 mg twice daily until the 90th day after stroke onset. Arm B included 435 patients who were administered a 300 mg loading dose of clopidogrel within 24 h after stroke symptoms, then continued on 75 mg per day until the 90th day after stroke onset.

Outcome Assessment

All the participants underwent thorough clinical assessment using the NIHSS and modified Rankin scale (mRS), which is a free single-item global outcome rating scale for determining post-stroke functionality in patients and which requires no formal training [23]. All patients underwent computerized tomography (CT)

and MRI imaging of brain vessels (including T1-weighted [T1W], T2W, fluid-attenuated inversion recovery [FLAIR], diffusion-weighted imaging [DWI], T2-weighted gradient echo, computed tomography angiography [CTA], or magnetic resonance angiography [MRA] if CTA was contraindicated) to rule out brain hemorrhage and confirm ischemic stroke diagnosis. We performed a follow-up brain CT 2 and 7 days after stroke to diagnose hemorrhagic infarction and assessed its type using the European Cooperative Acute Stroke Study (ECASS) classification [11, 24].

Follow-Up

During assessment for eligibility and before randomization, we performed a 12-lead routine ECG and transthoracic echocardiography (TTE) for all the participants to rule out heart failure, myocardial infarction, atrial fibrillation, and valvular heart diseases. After randomization and administering antiplatelet loading doses, we performed 24-h cardiac rhythm monitoring for each patient and found that five patients in the cilostazol group and four patients in the clopidogrel group had atrial fibrillation. These patients started anticoagulant therapy [25] and were included in the intention-to-treat analysis.

Each participant in our study underwent carotid duplex and basic laboratory tests, including a complete blood count, coagulation profile, lipid profile, blood glucose assessment, and liver function tests. We diagnosed diabetes when fasting plasma glucose level was greater than 126 mg/dl, casual plasma glucose was greater than 200 mg/dl, or HbA1C was more than 6.5 [26]. We evaluated blood pressure and diagnosed hypertension according to the 2020 International Society of Hypertension Global Hypertension Practice Guidelines when systolic blood pressure was greater than 140 mmHg and/or diastolic blood pressure was greater than 90 mm/Hg in two or more different office visit measurements [27].

We followed up with our participants for 90 days via telephone twice weekly and an interview once per month in our hospital. If any patient had recurrent stroke symptoms, we advised them to come to the hospital for brain imaging and assessment of their neurological 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.

Endpoints

Primary Endpoints

The primary efficacy endpoint of the study was the occurrence of a new stroke (either ischemic or hemorrhagic) within 90 days post-stroke [28]. We defined recurrent symptomatic ischemic stroke occurring during hospitalization as the occurrence of a new neurological manifestation or neurological deterioration associated with the following features: an increase in NIHSS score by more than 2 points, an increase in NIHSS sub-score 1a, 1b, or 1c by more than 1 point, or an increase in NIHSS sub-score 5a, 5b, 6a, or 6b by more than 1 point that was associated with new ischemic lesions on brain imaging. These manifestations had to persist for at least 24 h and were not related to edema, mass effect, brain shift syndrome, or hemorrhagic transformation of ischemic lesions [29]. We defined recurrent symptomatic ischemic stroke occurring after discharge from the hospital during the 3-month follow-up period as any ischemic stroke diagnosed by appropriate brain imaging and associated with an NIHSS score greater than 5 and/or an increase in the mRS score by 2 points or more in an otherwise fully recovered patient with previous stroke [12, 13]. We performed a follow-up brain CT 2 and 7 days post-stroke to diagnose hemorrhagic infarction and assessed its type using the European Cooperative Acute Stroke Study (ECASS) classification [11, 24].

The primary safety endpoint was the percentage of participants who experienced treatment-related hemorrhagic complications, evaluated using the Platelet Inhibition and Patient Outcomes (PLATO) bleeding definitions, which classify hemorrhagic complications into three types, as follows: (1) Major bleeding includes major life-threatening bleeding such as intracranial bleeding, intrapericardial bleeding with cardiac tamponade, and bleeding resulting

in hypovolemic shock or severe hypotension that requires the use of vasopressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin of more than 5 g/dL or requiring transfusion of ≥ 4 units of whole blood or packed red blood cells (PRBCs); other bleeding including significantly disabling events (e.g., intraocular with permanent vision loss), bleeding associated with a decrease in hemoglobin of 3–5 g/dL, or bleeding requiring transfusion of 2–3 units of whole blood or PRBCs. (2) Minor bleeding is defined as bleeding requiring medical intervention to stop or treat bleeding (e.g., epistaxis requiring a visit to a medical facility for packing). (3) Minimal bleeding includes all other bleeding (e.g., bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment [30].

Secondary Endpoints

The study had four secondary efficacy endpoints: the percentage of participants who experienced a composite of myocardial infarction, new stroke, or death due to vascular events within the follow-up period; the percentage of patients who experienced new ischemic stroke; the percentage of participants who had an unfavorable outcome with an mRS greater than 2 [31, 32] after 3 months; and the percentage of new symptomatic stroke (either ischemic or hemorrhagic) within 90 days post-stroke. The study had two secondary safety endpoints: the percentage of participants who experienced hemorrhagic transformation of brain infarction, where symptomatic hemorrhagic transformation of brain infarction was defined as parenchymal hematoma (PH) occurring following ischemic stroke and causing an increase in the NIHSS score by 4 points or more [33]; and the percentage of participants who experienced treatment-related side effects assessed via questionnaire.

Sample Size

We used PASS Power Analysis and Sample Size software (v 12, NCSS) to determine our sample size and detected that 826 patients would provide 90% power to determine a relative risk reduction of 50% in new stroke, either ischemic or hemorrhagic (primary outcome), in patients who received cilostazol compared to participants administered clopidogrel, with a final two-sided significance level of 95%, alpha error of 5%, assuming an incidence of new stroke of 14.1% [34] in patients who received clopidogrel and a dropout rate of 5%. We estimated our final sample size to be 870 patients, 435 in each arm.

Randomization and Blinding

An independent statistician developed a computer-based randomization chart with a four-block size, and the allocation sequences were repeated within a fixed block length of 4, so the two treatments, A and B, had six block sequences comprising AABB, BBAA, ABAB, BABA, ABBA, and BAAB. The participants were randomly assigned in a one-to-one ratio to receive either cilostazol or clopidogrel by a specially trained and qualified nurse. All investigators were blinded to the patients' assignments. We arranged consecutively numbered opaque sealed envelopes and 870 labels for each drug, labeled drug A or B. We utilized our randomization plan to sort the labels into envelopes numbered 1 to 870. The envelopes were distributed equally between the participating hospitals. The enrollment numbers assigned to patients began with 1 and were documented in their medical records. Next, we opened the files that matched the patient enrollment number, and according to the randomization, the patient was allocated to receive either drug A or B. Drug A was cilostazol 100 mg tablets, while drug B was clopidogrel 75 mg tablets.

The study was stratified by site, and each hospital recruited 145 patients. All the hospitals used the same allocation concealment method, which was sealed envelopes.

The trial did not include placebo due to limited financial resources. Instead, patients were instructed not to inform the examining neurologist about their medications but to inform the nurse. The nurse would inform

the physician if participants experienced medication-related side effects.

We conducted the follow-up visits, and a qualified nurse performed the follow-up calls. The participants were counseled to go to the hospital if they experienced medical deterioration.

We directed the nurses to strictly report every adverse effect, adherence issue, and clinical event reported by any patient. We did not use a placebo as we did not have funds from our university or the pharmaceutical companies to manufacture a placebo, owing to the economic crisis in Egypt, which has prevented many pharmaceutical companies from participating in clinical trials.

Statistical Analysis of the Data

A two-sided analysis of the data was performed by an independent statistician using the IBM SPSS software package (version 20.0, IBM Corp., Armonk, NY, USA). The analysis of safety and efficacy endpoints depended primarily on the intention-to-treat principle, and we also performed per-protocol analysis to evaluate the impact of drug discontinuation on the trial outcomes. We used the Shapiro–Wilk test to assess the distribution of the quantitative data. Data were expressed as mean ± SD if they were normally distributed or median and interquartile range (IQR) if they were non-normally distributed. We utilized the Mann–Whitney *U* test to compare the non-normally distributed quantitative data and Pearson's chi-square test to compare the qualitative data. We determined statistically significant variations between the two groups if the *P*-value was less than 0.05. As we had more than one secondary efficacy endpoint, we utilized Bonferroni correction to avoid type I statistical errors, and we regarded variations between the two groups as statistically significant if the *P*-value was less than 0.013. We also had two secondary safety outcomes, so we again utilized Bonferroni correction to avoid type I statistical error, and we considered variations between the two groups statistically significant if the *P*-value was less than 0.03. We performed the Kaplan–Meier test for survival analysis and the log-rank test to evaluate the effect of each treatment on the occurrence of different endpoints. The hazard ratio (HR) with a 95% confidence interval (CI) was calculated using Cox regression analysis, and the HR was considered significant if the CI did not include 1. We adjusted some patient characteristics in our Cox regression model, including previous TIA, number with prior antiplatelet treatment, gender, type of circulation affected, age, smoking status, dyslipidemia, diabetes mellitus, and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification of stroke.

RESULTS

We assessed the eligibility of 1340 patients to participate in our trial. Of those, 470 were not included in the randomization process for the following reasons: 42 patients had heart failure, 45 used cilostazol or clopidogrel regularly, 89 used anticoagulants regularly, 48 did not agree to be included in the trial, 21 were candidates for mechanical thrombectomy, 30 suffered from renal failure, 53 had thrombocytopenia with platelet count of < 100,000, 61 had an NIHSS score ≤ 3, 59 had an NIHSS score ≥ 25, and 22 had liver cell failure. Finally, 870 patients (661 [76%] male and 209 [24%] female) were assigned in a one-to-one ratio to receive either cilostazol or clopidogrel. A total of 829 patients completed the 3-month follow-up study, as shown in Fig. 1.

A total of 41 patients did not complete the study follow-up period, of which 20 patients (2.3%; seven in the cilostazol group and 13 in the clopidogrel group) developed major hemorrhagic complications, four patients (0.5%; two in each group) were lost to follow-up, eight patients (0.9%; five in the cilostazol group, three in the clopidogrel group) were not adherent to the treatment protocol as they received treatment irregularly, and nine patients (1%; five in the cilostazol group and four in the clopidogrel group) stopped our trial treatment prematurely and used other antiplatelet agents.

A total of 870 patients were included in the intention-to-treat analysis (435 patients in each group), and 849 patients were included

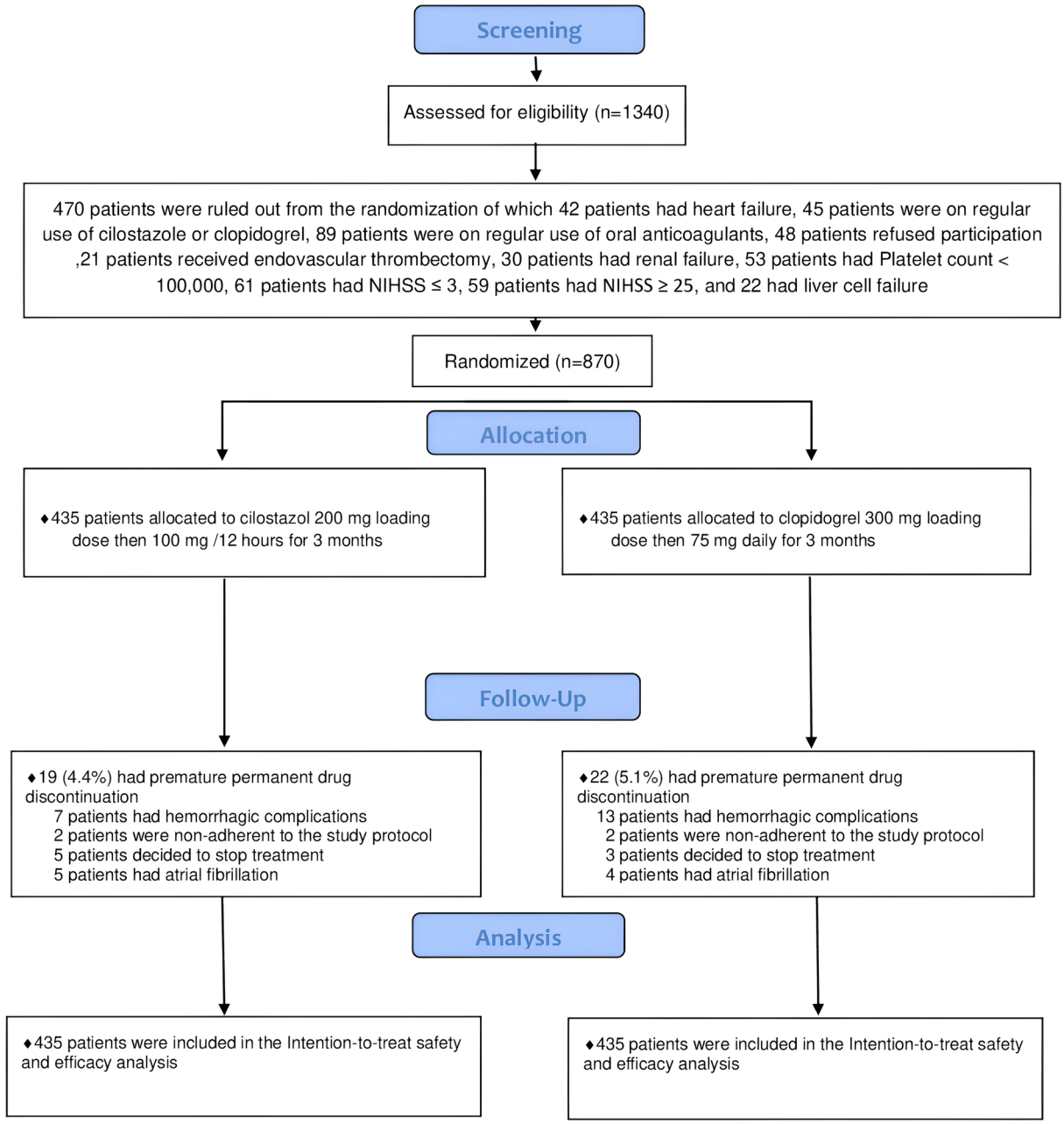


Fig. 1 Study flow diagram. NIHSS: National Institutes of Health Stroke Scale

in the per-protocol analysis (423 patients in the cilostazol group and 426 in the clopidogrel group).

We did not detect any significant abnormalities in the baseline features of the two groups, as shown in Table 1.

We found that 37 (8.5%) patients in the cilostazol group and 59 (13.6%) in the clopidogrel group experienced a new stroke (either hemorrhagic or ischemic) (HR 0.53; 95% CI, 0.33–0.84; $P=0.007$), as shown in Table 2 and Fig. 2.

Thirty-three (7.6%) patients in the cilostazol group and 49 (11.3%) in the clopidogrel group experienced a new ischemic stroke (HR 0.65; 95% CI, 0.42–1.02; $P=0.06$), while 57 (13.1%)

Table 1 Baseline characteristics for all participants

Characteristics	Cilostazol group ($n = 435$)	Clopidogrel group ($n = 435$)	*P*-value
Age (years), *n* (%)			
18–27	18.0 (4.1%)	13.0 (3.0%)	0.40
28–37	28.0 (6.4%)	23.0 (5.3%)	
38–47	70.0 (16.1%)	79.0 (18.2%)	
48–57	110.0 (25.3%)	100.0 (23.0%)	
58–67	94.0 (21.6%)	116.0 (26.7%)	
68–75	115.0 (26.4%)	104.0 (23.9%)	
Male, *n* (%)	335.0 (77.0%)	326.0 (74.9%)	0.48
Time to treatment, h, median (IQR)	8.5 (8.0–10.0)	8.5 (8.0–9.5)	0.58
Medical history, *n* (%)			
Smoker	228.0 (52.4%)	209.0 (48.0%)	0.20
Dyslipidemia	329.0 (75.6%)	318.0 (73.1%)	0.39
Diabetes mellitus	174.0 (40.0%)	156.0 (35.9%)	0.21
Hypertension	268.0 (61.6%)	284.0 (65.3%)	0.26
IHD	270.0 (62.1%)	286.0 (65.7%)	0.44
Baseline NIHSS, median (IQR)	11.0 (7–13)	11.0 (7–12)	0.37
TOAST classification, *n* (%)			
Small vessel occlusion	256.0 (58.9%)	266.0 (61.1%)	0.35
Stroke of undetermined etiology	31.0 (7.1%)	38.0 (8.7%)	
Large arterial atherosclerosis	148.0 (34.0%)	131.0 (30.1%)	
Previous TIA, *n* (%)	102.0 (23.4%)	94.0 (21.6%)	0.52
Prior antiplatelet treatment, *n* (%)	41.0 (9.4%)	51.0 (11.7%)	0.27
Prior statin treatment, *n* (%)	27.0 (6.2%)	21.0 (4.8%)	0.37
Anterior circulation stroke, *n* (%)	298.0 (68.5%)	287.0 (66.0%)	0.43

IHD ischemic heart disease; *IQR* interquartile range; *NIHSS* National Institutes of Health Stroke Scale; *TOAST* Trial of Org 10172 in Acute Stroke Treatment; *TIA* transient ischemic attack

patients in the cilostazol group and 77 (17.7%) in the clopidogrel group experienced a composite of a new stroke, MI, or death due to vascular insult (HR 0.72; 95% CI, 0.51–1.03; $P = 0.07$). In addition, 224 (51.5%) patients in the cilostazol group and 252 (57.9%) in the clopidogrel group had an unfavorable mRS score after 3 months (HR 0.69; 95% CI, 0.58–1.04; $P = 0.09$), and 19 (4.4%) patients in the cilostazol group and 32 (7.4%) in the clopidogrel group had recurrent symptomatic new stroke (either hemorrhagic or ischemic) (HR 0.47; 95% CI 0.37–0.79; *P* 0.01), as shown in Table 2.

Table 2 Analysis of efficacy and safety outcomes in all patients

Efficacy outcomes	Cilostazol group ($n = 435$)	Clopidogrel group ($n = 435$)	Hazard ratio (95% CI)	*P*-value
Primary efficacy outcome				
New stroke	37.0 (8.5%)	59.0 (13.6%)	0.53 (0.33–0.84)	0.007**
Secondary efficacy outcomes				
Composite of new stroke, MI, death	57.0 (13.1%)	77.0 (17.7%)	0.72 (0.51–1.03)	0.07
New ischemic stroke	33.0 (7.6%)	49.0 (11.3%)	0.65 (0.42–1.02)	0.06
Unfavorable outcome, mRS score of > 2 after 90 days	224 (51.5%)	252.0 (57.9%)	0.69 (0.58–1.04)	0.09
New symptomatic stroke	19.0 (4.4%)	32.0 (7.4%)	0.47 (0.37–0.79)	0.01**
Primary safety outcome				
Total hemorrhagic complications	12.0 (2.8%)	25.0 (5.7%)	0.25 (0.12–0.53)	0.001**
Secondary safety outcomes				
Total drug-related hemorrhagic transformation of infarction	4.0 (0.9%)	10.0 (2.3%)	0.34 (0.23– 0.74)	0.008**
Hemorrhagic infarction (HI) type 1 and 2	3.0 (0.7%)	4.0 (0.9%)	0.73 (0.63–1.13)	0.32
Parenchymal hematoma (PH) type 1 and 2	1.0 (0.2%)	6.0 (1.4%)	0.29 (0.25–0.67)	0.01**
Patients with drug-related non-hemorrhagic complications	43.0 (9.9%)	39.0 (9.0%)	0.81 (0.51–1.20)	0.41

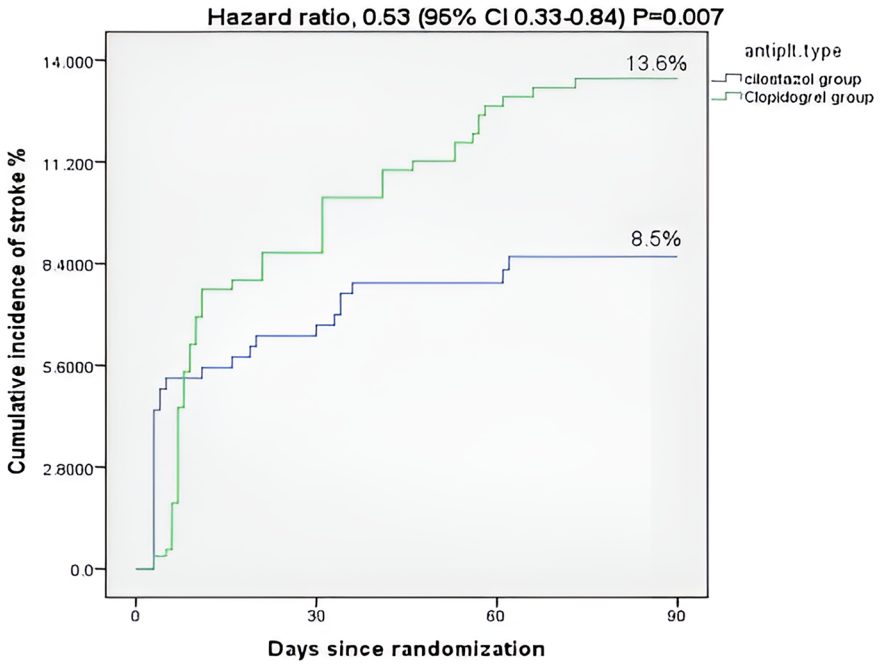
Incidence of recurrent stroke, composite event outcome, unfavorable outcome, hemorrhagic complications, and non-hemorrhagic complications determined by Kaplan–Meier estimates of the percentage of patients with events at 90 days

CI confidence interval; *MI* myocardial infarction; *mRS* modified Rankin scale

**Statistically significant at $P < 0.05$ for primary efficacy and primary safety outcomes; statistically significant at adjusted $P < 0.013$ for secondary efficacy outcomes; statistically significant at adjusted $P < 0.03$ for secondary safety outcomes

Eighteen (4.1%) patients in the cilostazol group and 26 (6.0%) in the clopidogrel group experienced recurrent symptomatic ischemic stroke (HR 0.49; 95% CI 0.53–1.03; *P* 0.08). Twelve patients (2.8%) in the cilostazol group experienced treatment-related hemorrhagic side effects, of which six participants had minimal hemorrhagic complications, two had minor hemorrhagic complications, and four had major hemorrhagic complications. In the clopidogrel arm, 25 participants (5.7%) experienced treatment-related hemorrhagic side effects, of which 11 had minimal hemorrhagic complications, four had minor hemorrhagic complications, and 10 experienced major hemorrhagic complications (HR 0.25; 95% CI, 0.12–0.53; $P = 0.001$) (Table 2, Fig. 3).

Forty-three (9.9%) patients in the cilostazol group experienced drug-related non-hemorrhagic side effects, of which 14 patients (3.2%) reported headache, eight (1.8%) suffered from diarrhea, 12 (2.8%) had palpitations, five (1.1%) had dizziness, nine (2.1%) had tachycardia, and four (0.9%) had nausea and vomiting. In comparison, 39 (9.0%) patients in the clopidogrel group had drug-related non-hemorrhagic side effects, of which 12 patients (2.8%) reported nausea and vomiting, seven (1.6%) had diarrhea, 10 (2.3%) experienced back pain, five (1.1%) had chest tightness, and



No. at risk				
Cilostazol	435	406	400	398
Clopidogrel	435	398	382	376

Fig. 2 Incidence of any stroke among all patients

seven (1.6%) had headache (HR 0.81; 95% CI, 0.51–1.20; *P*=0.41), as shown in Table 2.

Five patients in the cilostazol group and three patients in the clopidogrel group decided to stop treatment prematurely due to intolerable side effects, mainly headache and palpitations in the cilostazol group and nausea and vomiting in the clopidogrel group (HR 0.62; 95% CI, 0.47–1.13; *P*=0.26).

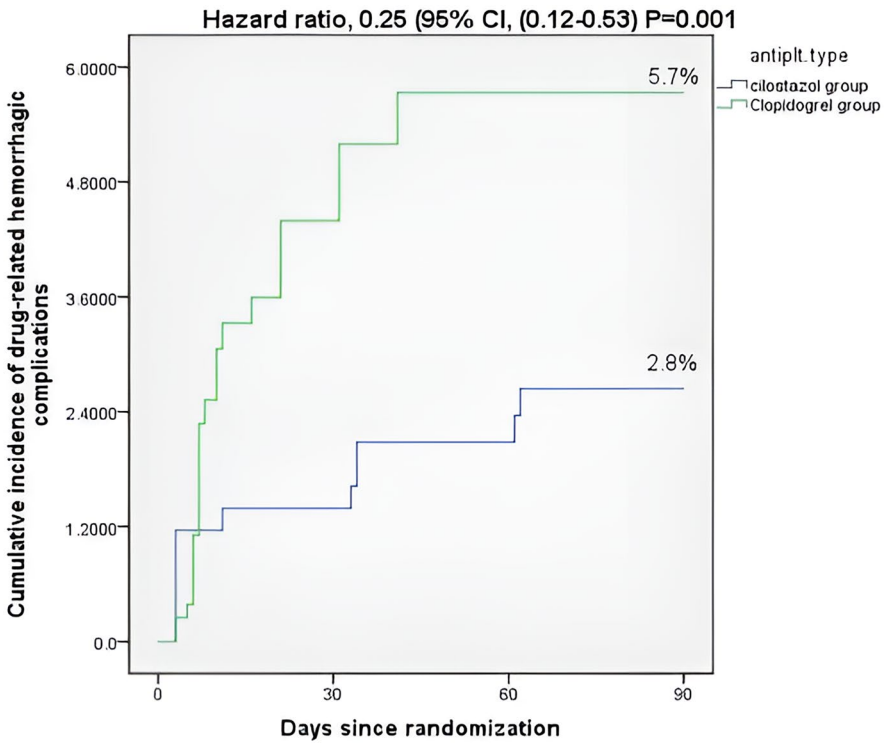
We performed a subgroup analysis to compare the safety and efficacy of cilostazol versus clopidogrel in hypertensive patients. We found that 24 (9%) patients in the cilostazol group and 40 (14.1%) in the clopidogrel experienced new stroke, either ischemic or hemorrhagic (HR 0.48; 95% CI, 0.28–0.82; *P*=0.007), as shown in Table 3 and Fig. 4.

We also found that 21 (7.8%) patients in the cilostazol group and 35 (12.3%) in the clopidogrel group had recurrent ischemic stroke (HR 0.48; 95% CI, 0.27–0.86; *P*=0.014), as shown in Table 3 and Fig. 5.

Twelve (4.5%) participants in the cilostazol arm and 19 (6.7%) in the clopidogrel group had recurrent symptomatic ischemic infarction (HR 0.42; 95% CI, 0.33–0.84; *P*=0.013).

Thirty-six (13.4%) participants in the cilostazol arm and 52 (18.3%) participants in the clopidogrel arm had a new stroke, MI, or death due to vascular insult (HR 1.35; 95% CI, 0.99–2.40; *P*=0.06), and 139 (51.9%) participants in the cilostazol arm and 165 (58.1%) in the clopidogrel arm had an unfavorable mRS score after 90 days (HR 1.42; 95% CI, 0.94–2.23; *P* 0.07). Also 13 (4.9%) participants in the cilostazol arm and 23 (8.1%) in the clopidogrel group had new symptomatic stroke (HR 0.38; 95% CI, 0.31–0.82; *P*=0.012), Table 3

Eight participants (3%) in the cilostazol group experienced treatment-related hemorrhagic side effects, of which four participants experienced minimal hemorrhagic complications, three had minor



No. at risk				
Cilostazol	435	429	426	423
Clopidogrel	435	416	411	410

Fig. 3 Hemorrhagic complications among all patients

hemorrhagic complications, and one had major hemorrhagic complications. In the clopidogrel arm, 17 participants (6%) had drug-related hemorrhagic complications, of which 11 patients had minimal bleeding, four had minor bleeding, and two experienced major bleeding (HR 0.21; 95% CI, 0.13–0.54; $P=0.02$), as shown in Table 3.

Twenty-seven (10.1%) patients in the cilostazol group had drug-related non-hemorrhagic side effects, of which eight patients (3.0%) had headache, five (1.9%) had diarrhea, eight (3.0%) had palpitations, two (0.7%) had dizziness, four (1.5%) had tachycardia, and two (0.7%) had nausea and vomiting. In comparison, 26 (9.2%) patients in the clopidogrel group had drug-related non-hemorrhagic side effects, of which eight patients (2.8%) had nausea and vomiting, five (1.6%) had diarrhea, seven (2.5%) had back pain, two (0.7%) had chest tightness, and four (1.4%) had headache (HR 0.67; 95% CI, 0.36–1.13; $P=0.37$), as shown in Table 3.

Three patients in the cilostazol group and two patients in the clopidogrel group decided to stop treatment prematurely due to intolerable side effects, mainly headache and palpitations in the cilostazol group and nausea and vomiting in the clopidogrel group (HR 0.57; 95% CI, 0.53–1.26; $P=0.34$).

In the per-protocol analysis, we found that 37 (8.7%) patients in the cilostazol group and 59 (13.8%) in the clopidogrel group experienced a new stroke (either hemorrhagic or ischemic) (HR 0.42; 95% CI, 0.38–0.89; $P=0.02$), as shown in Table 4.

Thirty-three (7.8%) patients in the cilostazol group and 49 (11.5%) in the clopidogrel group experienced a new ischemic stroke (HR 0.61; 95% CI, 0.49–1.08; $P=0.067$), while 57 (13.5%)

Table 3 Analysis of efficacy and safety outcomes in hypertensive patients

Efficacy outcomes	Cilostazol group ($n=268$)	Clopidogrel group ($n=284$)	Hazard ratio (95% CI)	*P*-value
Primary efficacy outcome				
New stroke	24.0 (9.0%)	40.0 (14.1%)	0.48 (0.28–0.82)	0.007**
Secondary efficacy outcomes				
Composite of new stroke, MI, death	36.0 (13.4%)	52.0 (18.3%)	1.53 (0.99–2.40)	0.06
New ischemic stroke	21.0 (7.8%)	35.0 (12.3%)	0.48 (0.27–0.86)	0.014**
Unfavorable outcome, mRS score > 2 after 90 days	139 (51.9%)	165.0 (58.1%)	1.42 (0.94–2.23)	0.07
New symptomatic stroke	13.0 (4.9%)	23.0 (8.1%)	0.38 (0.31–0.82)	0.012**
Primary safety outcome				
Total hemorrhagic complications	8.0 (3.0%)	17.0 (6.0%)	0.21 (0.13–0.54)	0.02**
Secondary safety outcomes				
Drug-related hemorrhagic transformation of infarction	3.0 (1.1%)	7.0 (2.5%)	0.31 (0.15- 0.53)	0.02**
Hemorrhagic infarction (HI) type 1 and 2	2.0 (0.7%)	3.0 (1.1%)	0.62 (0.58–1.27)	0.53
Parenchymal hematoma (PH) type 1 and 2	1.0 (0.4%)	4.0 (1.4%)	0.27 (0.22–0.61)	0.03**
Drug-related non-hemorrhagic complications	27.0 (10.1%)	26.0 (9.2%)	0.67 (0.36–1.13)	0.37

Incidence of recurrent stroke, composite event outcome, unfavorable outcome, hemorrhagic complications, and non-hemorrhagic complications determined by Kaplan–Meier estimates of the percentage of patients with events at 90 days

CI confidence interval; *mRS* modified Rankin scale

**Statistically significant at $P<0.05$ for primary efficacy and primary safety outcomes; statistically significant at adjusted $P<0.013$ for secondary efficacy outcomes; statistically significant at adjusted $P<0.03$ for secondary safety outcomes

patients in the cilostazol group and 77 (18.1%) in the clopidogrel group had a composite of a new stroke, MI, or death due to vascular insult (HR 0.64; 95% CI, 0.63–1.11; $P=0.08$). A total of 224 (53%) patients in the cilostazol group and 252 (59.2%) in the clopidogrel group had an unfavorable mRS score after 3 months (HR 0.54; 95% CI, 0.61–1.09; *P* 0.08), and 19 (4.5%) patients in cilostazol group and 32 (7.5%) in clopidogrel group had a recurrent symptomatic new stroke (either hemorrhagic or ischemic) (HR 0.41; 95% CI 0.38–0.82; *P* 0.011), as shown in Table 4.

Twelve participants (2.8%) in the cilostazol group experienced treatment-related hemorrhagic side effects, of which six participants had minimal hemorrhagic complications, two had minor hemorrhagic complications, and four participants had major hemorrhagic complications. In the clopidogrel arm, 25 participants (5.7%) had treatment-related hemorrhagic side effects, of which 11 patients had minimal hemorrhagic complications, four had minor hemorrhagic complications, and 10 experienced major hemorrhagic complications (HR 0.23; 95% CI, 0.19–0.63; $P=0.006$), Table 4.

Forty-three (10.2%) patients in the cilostazol group and 39 (9.2%) in the clopidogrel group experienced drug-related non-hemorrhagic side effects (HR 0.74; 95% CI, 0.47–1.28; $P=0.43$), as shown in Table 4.

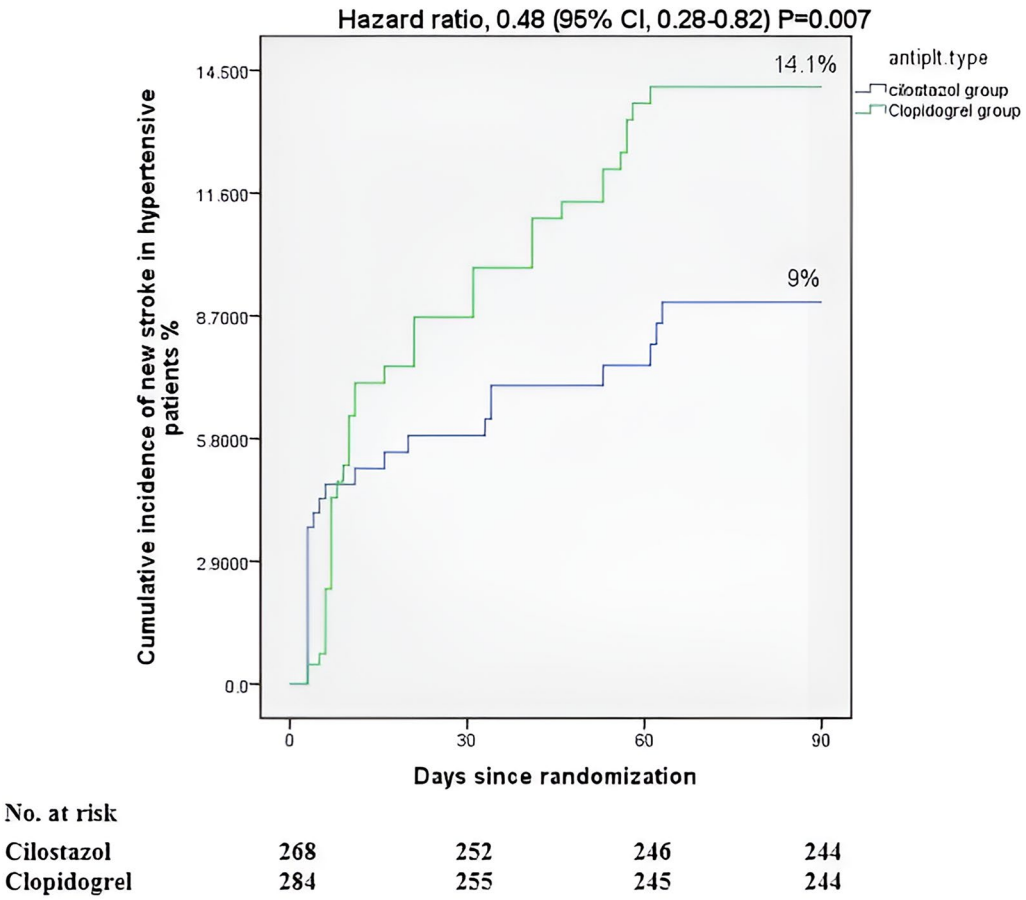


Fig. 4 Incidence of any stroke in hypertensive patients

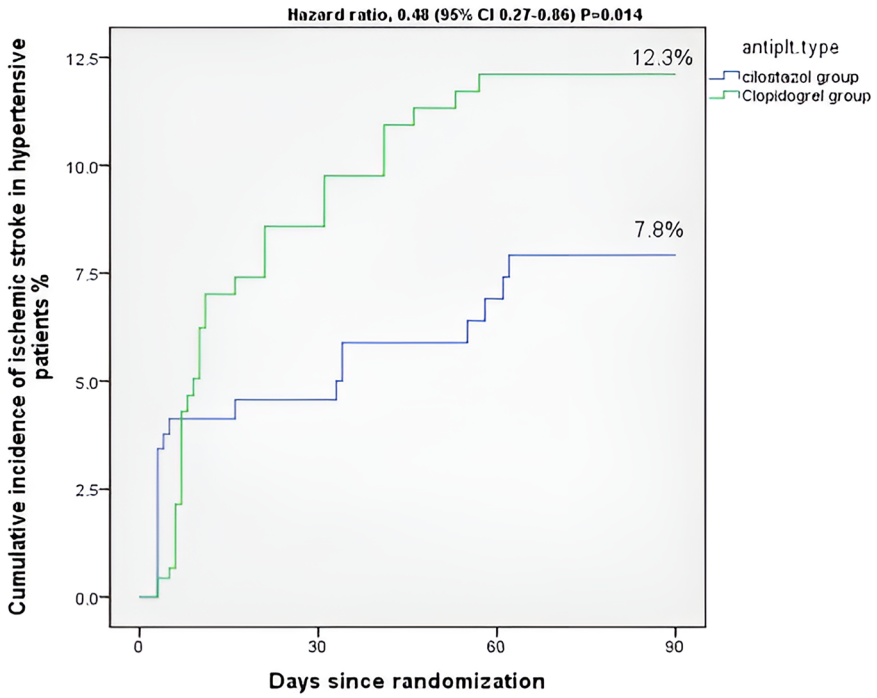
DISCUSSION

Cilostazol is a selective, reversible phosphodiesterase III (PDE-III) inhibitor that increases cyclic adenosine monophosphate (cAMP) levels in platelets, leading to improving endothelial cell function and reducing the number of platelets partially activated by interacting with activated endothelial cells [35, 36]. Cilostazol inhibits shear stress-induced platelet aggregation and enhances the antiplatelet effects of the endothelium-derived prostacyclin (PGI2), which inhibits intra-arterial thrombosis [37, 38].

Although cilostazol is widely used in some parts of Asia, it is not commonly used in Africa, Europe, or the USA due to its unavailability, higher cost than aspirin, and unfamiliarity of physicians with cilostazol [39].

Our study focused on evaluating the efficacy and safety of cilostazol in patients with moderate and moderate-to-severe ischemic stroke to support the tailored use of antiplatelet agents such as cilostazol, which has a lower risk of hemorrhagic complications, especially in patients with large infarction core and high baseline NIHSS score, such as moderate and moderate-to-severe stroke, which has a higher incidence of hemorrhagic complications [11].

Our study included patients with moderate-to-severe stroke and excluded those with minor stroke, as moderate-to-severe strokes differ from minor strokes in treatment and outcomes, with secondary prevention of minor stroke necessitating dual antiplatelet therapy for 3 weeks up to 3 months, while we used



No. at risk				
Cilostazol	268	255	249	247
Clopidogrel	284	259	250	249

Fig. 5 Incidence of ischemic stroke in patients with hypertension

single antiplatelet agents for secondary stroke prevention in patients with moderate-to-severe stroke [40]. Also, moderate-to-severe stroke is characterized by a higher NIHSS score than minor stroke, which is associated with a higher incidence of hemorrhagic complications and poor functional outcomes [41–46].

We followed up with patients for 3 months in accord with many major stroke trials, such as SOCRATES and CHANCE 2, which used 3 months as their standard follow-up period [47, 48].

Some studies showed that CYP2C19 loss-of-function alleles occur in about 5% of Africans [49]. Other studies reported that the North African populations occupy an intermediate position between European and Asian populations regarding the prevalence of the three CYP2C genes polymorphism [50]. We did not perform the genetic test for CYP2C19 loss-of-function alleles, as we did not have sufficient funds for genetic testing. In addition, a genetic subgroup analysis of the PLATO trial demonstrated that ticagrelor yielded better results than clopidogrel in acute coronary syndromes despite the CYP2C19 genotype [51].

We performed per-protocol and intention-to-treat analysis to evaluate the impact of drug discontinuation on the trial outcomes. We found that treatment discontinuation did not affect the outcome, and the per-protocol analysis confirmed the intention-to-treat results.

In our trial, the cilostazol group had statistically significantly less frequent new strokes (ischemic and hemorrhagic) and less frequent hemorrhagic transformation of brain infarction and systemic hemorrhagic side effects than the clopidogrel group. This agrees with the findings of Liu et al., who showed that the use of cilostazol was associated with less frequent

Table 4 Per-protocol analysis of efficacy and safety outcomes in all patients

Efficacy outcomes	Cilostazol group ($n = 423$)	Clopidogrel group ($n = 426$)	Hazard ratio (95% CI)	*P*-value
Primary efficacy outcome				
New stroke	37.0 (8.7%)	59.0 (13.8%)	0.42 (0.38–0.89)	0.02**
Secondary efficacy outcomes				
Composite of new stroke, MI, death	57.0 (13.5%)	77.0 (18.1%)	0.64 (0.63–1.11)	0.08
New ischemic stroke	33.0 (7.8%)	49.0 (11.5%)	0.61 (0.49–1.08)	0.07
Unfavorable outcome, mRS score of > 2 after 90 days	224 (53%)	252.0 (59.2%)	0.54 (0.61–1.09)	0.08
New symptomatic stroke	19.0 (4.5%)	32.0 (7.5%)	0.41 (0.38–0.82)	0.011**
Primary safety outcome				
Total hemorrhagic complications	12.0 (2.8%)	25.0 (5.9%)	0.23 (0.19–0.63)	0.006**
Secondary safety outcomes				
Total drug-related hemorrhagic transformation of infarction	4.0 (0.9%)	10.0 (2.3%)	0.31 (0.29–0.81)	0.01**
Hemorrhagic infarction (HI) type 1 and 2	3.0 (0.7%)	4.0 (0.9%)	0.69 (0.72–1.24)	0.29
Parenchymal hematoma (PH) type 1 and 2	1.0 (0.2%)	6.0 (1.4%)	0.22 (0.31–0.78)	0.02**
Drug-related non-hemorrhagic complications	43.0 (10.2%)	39.0 (9.2%)	0.74 (0.47–1.28)	0.43
Patients who discontinued treatment without clinical indications	12.0 (2.8%)	9.0 (2.1%)	0.66 (0.49–1.13)	0.49

Incidence of recurrent stroke, composite event outcome, unfavorable outcome, hemorrhagic complications, and non-hemorrhagic complications determined by Kaplan–Meier estimates of the percentage of patients with events at 90 days

CI confidence interval; *MI* myocardial infarction; *mRS* modified Rankin scale

**Statistically significant at $P < 0.05$ for primary efficacy and primary safety outcomes; statistically significant at adjusted $P < 0.013$ for secondary efficacy outcomes; statistically significant at adjusted $P < 0.03$ for secondary safety outcomes

hemorrhagic transformation of stroke [52]. However, our findings differ from those of Kwon et al. [53] and Lee et al. [54], who found no significant difference in the rates of hemorrhagic transformation of brain infarction between cilostazol and clopidogrel groups. In our study, there were no significant differences in the rate of recurrent ischemic stroke, the rate of myocardial infarction, or death due to vascular complications between the two arms. These findings agreed with Kwon et al. [53], Lee et al. [54], and Lee et al. [55], who found no significant difference in efficacy and safety between cilostazol and clopidogrel in secondary prevention of ischemic stroke.

The ability of cilostazol to reduce the incidence of new recurrent stroke without significantly increasing hemorrhagic complications either centrally or peripherally compared to clopidogrel can be explained by the fact that cilostazol functions as an endothelium-targeted antithrombotic therapy, exerting its action by improving endothelial cell function and reducing the number of activated platelets. Cilostazol inhibits primary and secondary platelet aggregation induced by collagen, adenosine diphosphate (ADP), and arachidonic

acid, with a negligible effect on bleeding time and a relatively short recovery time for platelet function. In contrast, clopidogrel irreversibly blocks the ADP P2Y12 receptor on platelets and prevents platelet aggregation, resulting in longer bleeding time [56–58].

Many other trials have shown a minimal effect of cilostazol on bleeding time. For example, a study evaluating the impact of cilostazol, aspirin, and ticlopidine on bleeding time in healthy men showed that bleeding time was significantly prolonged with aspirin and ticlopidine. In contrast, cilostazol did not affect total blood loss or bleeding rate [58]. Other studies assessing platelet function in patients with peripheral arterial disease showed that aspirin and clopidogrel significantly prolonged bleeding time when used either individually or in combination. In contrast, cilostazol did not significantly increase the bleeding time [56].

In addition, the better safety outcomes in the cilostazol group in our study regarding hemorrhagic complications differed from the findings of Kwon et al. [53], Lee et al. [54], and Lee et al. [55]. These studies were all performed in Asian patients, while our trial included white patients from Egypt, and there are variations between Asian and white patients regarding hemostasis. Moreover, Asians are at higher risk of bleeding and lower risk of thrombotic complications than Caucasians [56]. Some genetic differences could partially explain these findings, such as factor V Leiden, a thrombotic polymorphism in factor V common in white populations, which was not found in any Japanese persons included in a wide-scale epidemiological study [59]. In addition, for Japanese patients with atrial fibrillation, the risk of hemorrhagic complications increases markedly if the international normalized ratio (INR) is greater than 2 [60]. In contrast, in white patients with atrial fibrillation, the target INR is from 2 to 3 [61].

Our subgroup analysis showed that patients with hypertension who received cilostazol had statistically significantly lower rates of ischemic stroke, hemorrhagic transformation of brain infarction, and drug-related hemorrhagic complications. Our results agreed with those of Lee et al., who found that cilostazol significantly reduced the risk of recurrent ischemic stroke compared to clopidogrel. This can be explained by the fact that cilostazol produces vasodilation and suppresses angiotensin 2-induced hypertensive endothelial dysfunction, leading to decreased systolic blood pressure during the follow-up period and eventually enhanced protection against stroke recurrence [62].

In our discussion, we mentioned studies that were slightly different from the setting of our trial, such as studies that compared cilostazol versus clopidogrel in Asians, evaluated a dual antiplatelet regimen by comparing cilostazol and aspirin versus clopidogrel and aspirin, or included patients with intracranial atherosclerosis or carotid stenosis, to demonstrate the similarities and differences between the outcomes of using cilostazol versus clopidogrel as single antiplatelet agents in patients of different ethnicity (African patients) and different stroke severity (moderate and moderate-to-severe stroke).

Our trial showed better safety results for cilostazol than the THALES trial, which compared aspirin and ticagrelor versus aspirin alone in patients with minor stroke or TIA, and showed that about 1.2% of patients who received ticagrelor experienced hemorrhagic infarction, while in our study only 0.9% of patients who received cilostazol experienced hemorrhagic infarction [63]. Also, the POINT trial, which compared aspirin and clopidogrel versus aspirin alone in patients with minor stroke or TIA, showed that about 1.0% of patients who received ticagrelor experienced intracranial hemorrhage, while in our study only 0.9% of patients who received cilostazol experienced hemorrhagic infarction [64].

Although the absolute risk reduction (ARR) for recurrent stroke and treatment-related hemorrhagic complications in the cilostazol group was small, the reduction in mortality and morbidity associated with recurrent stroke and antiplatelet-related hemorrhagic complications was high, and given the recent availability of cilostazol and clopidogrel in the Egyptian insurance system, our findings would lead us to recommend the use of cilostazol over clopidogrel, as it offers a better chance than clopidogrel for reducing the incidence of

treatment-related hemorrhagic complications in Egyptian patients with moderate and moderate-to-severe ischemic stroke.

Although our trial has some advantages, it had some limitations: The single-blinded design is a key limitation, mainly because it may introduce performance and detection bias in reporting side effects. Second, all of our participants were Egyptian, which limited our ability to the assess different ethnicities with a diverse genetic background. Third, the relatively short follow-up duration does not permit us to evaluate the long-term results of our treatment, and fourth, the findings in the hypertensive group were extracted from post hoc analysis, which is vulnerable to data dredging.

In the future, further multicenter, double-blinded studies are needed that include broader ethnicities and involve a more extended follow-up period of more than 1 year.

CONCLUSION

Egyptian patients with non-cardioembolic moderate and moderate-to-severe ischemic stroke who received cilostazol within the first 24 h of symptoms had significantly lower rates of hemorrhagic transformation of brain infarction and peripheral hemorrhagic complications than those who received clopidogrel. Patients with hypertension achieved the best benefit from cilostazol, as they experienced a significant reduction in recurrent ischemic and hemorrhagic infarction. No significant differences were observed between the two groups regarding mRS after 3 months or non-hemorrhagic side effects.

Our results were derived from a single-blinded study; therefore, a more extensive, double-blinded, multinational study is needed for the results to be generalizable worldwide.

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Authors' Contributions. Dr. Mohamed G. Zeinhom and Dr. Sherihan Rezk Ahmed were the principal investigators who collected data. Dr. Mohamed Ismaiel, Dr. Mohamed Fouad elsayed Khalil, Dr. Mohamed Ahmed Almoataz, Dr. Tarek youssif omar, Dr. Ahmed Mohamed ali Daabis, Dr. Hossam Mohamed Refat, Dr. Ahmed ahmed Mohamed kamal ebied, Dr. Noha Abdelwahed, Dr. Ahmed Zaki Omar Akl, and Dr. Salah Ibrahim Ahmed shared in developing the study design and concept. Dr. Emad Labib Abdelhamid Mahmoud evaluated the cardiological condition of the trial patients, while Dr. Mohamed G. Zeinhom and Dr. Sherihan Rezk Ahmed shared in manuscript drafting. All authors revised the manuscript.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Dr. Mohamed G. Zeinhom, Dr. Mohamed Ismaiel, Dr. Mohamed Fouad elsayed Khalil, Dr. Mohamed Ahmed Almoataz, Dr. Tarek youssif omar, Dr. Ahmed Mohamed ali Daabis, Dr. Hossam Mohamed Refat, Dr. Ahmed ahmed Mohamed kamal ebied, Dr. Noha Abdelwahed, Dr. Ahmed Zaki Omar Akl, Dr. Emad Labib Abdelhamid Mahmoud, Dr. Salah Ibrahim Ahmed, Dr. Sherihan Rezk Ahmed have nothing to disclose.

Ethical Approval. Our study was approved by the ethical committee of Kafr El-sheikh University (reference number KFSIRB200-145). We obtained formal written consent from the patients or their first of kin if the patients were illiterate or critically ill. The data reported herein do not contain any identifiable information regarding our patients.

REFERENCES

1. Zeinhom MG, Elbassiouny A, Mahmoud A, Sherihan M, Ahmed R. Ticagrelor versus clopidogrel in acute large-vessel ischemic stroke: a randomized controlled single-blinded trial. CNS Drugs. 2024;38(5):387–93. https://doi.org/10.1007/s40263-024-01080-5.

2. Aref HM, El-Khawas H, Elbassiouny A, Shokri HM, Zeinhom MG, Roushdy TM. A randomized pilot study of the efficacy and safety of loading ticagrelor in acute ischemic stroke. Neurol Sci. 2023;44(2):765–71. https://doi.org/10.1007/s10072-022-06525-7.

3. Powers WJ, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke. Stroke. 2019;50(12):e344–418. https://doi.org/10.1161/STR.0000000000000211.

4. Zeinhom MG, et al. Predictors of the unfavorable outcomes in acute ischemic stroke patients treated with alteplase, a multi-center randomized trial. Sci Rep. 2024;14(1):1–9. https://doi.org/10.1038/s41598-024-56067-5.

5. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared. Stroke. 2009;40(6):2068–72. https://doi.org/10.1161/STROKEAHA.108.540112.

6. Tani T, Sakurai K, Kimura Y, Ishikawa T, Hidaka H. Pharmacological manipulation of tissue cyclic AMP by inhibitors. Effects of phosphodiesterase inhibitors on the functions of platelets and vascular endothelial cells. Adv Second Messenger Phosphoprotein Res. 1992;25:215–27.

7. Rondina MT, Weyrich AS. Targeting phosphodiesterases in anti-platelet therapy. Handb Exp Pharmacol. 2012;210:225–38. https://doi.org/10.1007/978-3-642-29423-5_9.

8. Volney C, Collins A, Adams S. Ticagrelor versus clopidogrel in the management of acute myocardial infarction. J Commun Hosp Intern Med Perspect. 2019;9(4):314–8. https://doi.org/10.1080/20009666.2019.1644915.

9. Winter MP, Koziński M, Kubica J, Aradi D, Siller-Matula JM. Personalized antiplatelet therapy with P2Y12 receptor inhibitors: benefits and pitfalls. Postep w Kardiol Interwencyjnej. 2015;11(4):259–80. https://doi.org/10.5114/pwki.2015.55596.

10. McHutchison C, et al. Cilostazol for secondary prevention of stroke and cognitive decline: systematic review and meta-analysis. Stroke. 2020;51(8):2374–85. https://doi.org/10.1161/STROKEAHA.120.029454.

11. Zeinhom MG, et al. A multicenter trial on the predictors of different subtypes of hemorrhagic infarction after thrombolysis. Sci Rep. 2024;14(1):29822. https://doi.org/10.1038/s41598-024-76189-0.

12. Julie Fussner CV. Assessing stroke—scores & scales. Am. Stroke Assoc., pp. 1–23; 2019. https://www.heart.org/-/media/files/affiliates/gra/gra-qsi/2019-scbc-presentations/5-assessing-stroke-scores-scales-v2.pdf?la=en

13. Kogan E, Twyman K, Heap J, Milentijevic D, Lin JH, Alberts M. Assessing stroke severity using electronic health record data: a machine learning approach. BMC Med Inform Decis Mak. 2020;20(1):8. https://doi.org/10.1186/s12911-019-1010-x.

14. Zeinhom MG, Aref HM, El-Khawas H, Roushdy TM, Shokri HM, Elbassiouny A. A pilot study of the ticagrelor role in ischemic stroke secondary prevention. Eur Neurol. 2022;85(1):50–5. https://doi.org/10.1159/000518786.

15. Matsuoka S, et al. Age modified relationship between modifiable risk factors and the risk of atrial fibrillation. Circ Arrhythmia Electrophysiol.

2022;15(1): e010409. https://doi.org/10.1161/CIRCEP.121.010409.

16. Mentz RJ, et al. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. JAMA. 2023;329(3):214–23. https://doi.org/10.1001/jama.2022.23924.

17. Zeller T, Trenk D. Cilostazol. Circulation. 2013;127(23):2261–3. https://doi.org/10.1161/CIRCULATIONAHA.113.003284.

18. Hart RG, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429–38. https://doi.org/10.1016/S1474-4422(13)70310-7.

19. Ntaios G, Hart RG. Embolic stroke. Circulation. 2017;136(25):2403–5. https://doi.org/10.1161/CIRCULATIONAHA.117.030509.

20. Hindricks G, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373–498. https://doi.org/10.1093/eurheartj/ehaa612.

21. De Havenon A, et al. Cilostazol for secondary stroke prevention: history, evidence, limitations, and possibilities. Stroke. 2021;52(10):E635–45. https://doi.org/10.1161/STROKEAHA.121.035002.

22. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel–drug interactions. J Am Coll Cardiol. 2011;57(11):1251–63. https://doi.org/10.1016/j.jacc.2010.11.024.

23. Weimar C, et al. Assessment of functioning and disability after ischemic stroke. Stroke. 2002;33(8):2053–9. https://doi.org/10.1161/01.str.0000022808.21776.bf.

24. Rezk S, Nevine A, Nahas E, Fouad M, Khalil E, Elbassiouny A. TICA-CLOP STUDY: ticagrelor versus clopidogrel in acute moderate and moderate-to-severe ischemic stroke, a randomized controlled multi-center trial. CNS Drugs. 2024;39(1):81–93. https://doi.org/10.1007/s40263-024-01127-7.

25. De Marchis GM, et al. New avenues for optimal treatment of atrial fibrillation and stroke prevention. Stroke. 2021;52(4):1490–9. https://doi.org/10.1161/STROKEAHA.120.032060.

26. Elgamal S, Ahmed SR, Nahas MM, Hendawy SR, Elshafei O, Zeinhom MG. The effect of lacosamide on calcitonin gene-related peptide serum level in episodic migraine patients: a randomized, controlled trial. Acta Neurol Belg. 2024;124(3):965–72. https://doi.org/10.1007/s13760-024-02499-9.

27. Unger T, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334–57. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026.

28. Liu L, et al. Dual antiplatelet therapy in stroke and ICAS: subgroup analysis of CHANCE. Neurology. 2015;85(13):1154–62.

29. Park TH, et al. Neurologic deterioration in patients with acute ischemic stroke or transient ischemic attack. Neurology. 2020. https://doi.org/10.1212/WNL.0000000000010603.

30. Schulman S, Anger SU, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8(1):202–4. https://doi.org/10.1111/j.1538-7836.2009.03678.x.

31. Furlan AJ. Acute stroke trials: strengthening the underpowered. Stroke. 2002;33(6):1450–1. https://doi.org/10.1161/01.STR.0000018645.04200.7D.

32. Wang C, et al. Ticagrelor versus clopidogrel in minor stroke or transient ischemic attack with intracranial artery stenosis: a post hoc analysis of CHANCE-2. J Am Heart Assoc. 2023;12(21):1–12. https://doi.org/10.1161/JAHA.123.031611.

33. Köhrmann M, Schellinger PD. Symptomatic intracranial hemorrhage after thrombolysis. Cerebrovasc Dis (Basel, Switzerland). 2007;23(2–3):83–4. https://doi.org/10.1159/000097042.

34. Chimowitz MI, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365(11):993–1003. https://doi.org/10.1056/NEJMoa1105335.

35. Gotoh F, et al. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2000;9(4):147–57. https://doi.org/10.1053/jscd.2000.7216.

36. Umekawa H, Tanaka T, Kimura Y, Hidaka H. Purification of cyclic adenosine monophosphate phosphodiesterase from human platelets using new-inhibitor sepharose chromatography. Biochem Pharmacol. 1984;33(21):3339–44. https://doi.org/10.1016/0006-2952(84)90103-5.

37. Minami N, et al. Inhibition of shear stress-induced platelet aggregation by cilostazol, a specific inhibitor of cGMP-inhibited phosphodiesterase, in vitro and ex vivo. Life Sci. 1997;61(25):383–9. https://doi.org/10.1016/s0024-3205(97)00986-7.

38. Igawa T, et al. Potentiation of anti-platelet aggregating activity of cilostazol with vascular endothelial cells. Thromb Res. 1990;57(4):617–23. https://doi.org/10.1016/0049-3848(90)90079-r.

39. Kim JS, Kwon SU, Uchiyama S. Cilostazol research in Asia: can it be applied to European and American patients? Int J Stroke Off J Int Stroke Soc. 2015;10(Suppl 1):1–9. https://doi.org/10.1111/ijs.12460.

40. Powers WJ, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018. https://doi.org/10.1161/STR.0000000000000158.

41. Chenna V, et al. Predictors of intracerebral hemorrhage in acute stroke patients receiving intravenous recombinant tissue plasminogen activator. Ann Indian Acad Neurol. 2018;21(3):214–9. https://doi.org/10.4103/aian.AIAN_228_17.

42. Dorňák T, et al. Posterior vs. anterior circulation infarction: demography, outcomes, and frequency of hemorrhage after thrombolysis. Int J Stroke. 2015;10(8):1224–8. https://doi.org/10.1111/ijs.12626.

43. Sun F, et al. Predictive factors of hemorrhage after thrombolysis in patients with acute ischemic stroke. Front Neurol. 2020;11(November):1–6. https://doi.org/10.3389/fneur.2020.551157.

44. Xue Y, et al. Predictors for symptomatic intracranial hemorrhage after intravenous thrombolysis with acute ischemic stroke within 6 h in northern China: a multicenter, retrospective study. BMC Neurol. 2022;22(1):1–7. https://doi.org/10.1186/s12883-021-02534-9.

45. Aoki J, et al. NIHSS-time score easily predicts outcomes in rt-PA patients: the SAMURAI rt-PA registry. J Neurol Sci. 2013;327(1–2):6–11. https://doi.org/10.1016/j.jns.2013.01.029.

46. Elsayed MA, Salah H, Sabbah A, Hatem G, Moawad MK. Early functional outcome after IV rTPA administration in Egyptian acute ischemic stroke patients. Egypt J Neurol Psychiatry Neurosurg. 2019. https://doi.org/10.1186/s41983-019-0110-y.

47. Johnston SC, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med. 2016;375(1):35–43. https://doi.org/10.1056/nejmoa1603060.

48. Wang Y, et al. Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. N Engl J Med. 2021;385(27):2520–30. https://doi.org/10.1056/nejmoa2111749.

49. Dehbozorgi M, et al. Prevalence of the CYP2C19*2 (681 G>A), *3 (636 G>A) and *17 (-806 C>T) alleles among an Iranian population of different ethnicities. Mol Med Rep. 2018;17(3):4195–202. https://doi.org/10.3892/mmr.2018.8377.

50. Messaoudi M, Pakstis AJ, Boussetta S, Ben Ammar Elgaaied A, Kidd KK, Cherni L. CYP2C gene polymorphisms in North African populations. Mol Biol Rep. 2024;51(1):1145. https://doi.org/10.1007/s11033-024-10093-8.

51. Liu L, et al. Dual antiplatelet therapy in stroke and ICAS: subgroup analysis of CHANCE. Neurology. 2015;85(13):1154–62. https://doi.org/10.1212/WNL.0000000000001972.

52. Liu H, et al. Comparison of cilostazol versus clopidogrel in addition to aspirin in patients with ischemic stroke who underwent intracranial or extracranial artery stent implantation. J Atheroscler Thromb. 2023;30(8):1010–21. https://doi.org/10.5551/jat.63632.

53. Kwon SU, et al. Efficacy and safety of combination antiplatelet therapies in patients with symptomatic intracranial atherosclerotic stenosis. Stroke. 2011;42(10):2883–90. https://doi.org/10.1161/STROKEAHA.110.609370.

54. Lee TH, Lin YS, Liou CW, Der Lee J, Peng TI, Liu CH. Comparison of long-term efficacy and safety between cilostazol and clopidogrel in chronic ischemic stroke: a nationwide cohort study. Ther Adv Chronic Dis. 2020;11:1–14. https://doi.org/10.1177/2040622320936418.

55. Lee YJ, Je NK. Long-term effectiveness and safety of cilostazol versus clopidogrel in secondary prevention of noncardioembolic ischemic stroke. Eur J Clin Pharmacol. 2023;79(8):1107–16. https://doi.org/10.1007/s00228-023-03522-3.

56. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. Atheroscler Suppl. 2005;6(4):3–11. https://doi.org/10.1016/j.atherosclerosissup.2005.09.002.

57. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. J Vasc Surg. 2003;38(4):710–3. https://doi.org/10.1016/s0741-5214(03)01029-2.

58. Tamai Y, Takami H, Nakahata R, Ono F, Munakata A. Comparison of the effects of acetylsalicylic acid, ticlopidine and cilostazol on primary hemostasis

using a quantitative bleeding time test apparatus. Haemostasis. 1999;29(5):269–76. https://doi.org/10.1159/000022512.

59. de Moerloose P, Reber G, Perrier A, Perneger T, Bounameaux H. Prevalence of factor V Leiden and prothrombin G20210A mutations in unselected patients with venous thromboembolism. Br J Haematol. 2000;110(1):125–9. https://doi.org/10.1046/j.1365-2141.2000.02039.x.

60. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation : a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Stroke. 2000;31(4):817–21. https://doi.org/10.1161/01.str.31.4.817.

61. Fuster V, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee. J Am Coll Cardiol. 2001;38(4):1231–66. https://doi.org/10.1016/s0735-1097(01)01587-x.

62. Shi M-Q, et al. Cilostazol suppresses angiotensin II-induced apoptosis in endothelial cells. Mol Med Rep. 2016;13(3):2597–605. https://doi.org/10.3892/mmr.2016.4881.

63. Johnston SC, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. N Engl J Med. 2020;383(3):207–17. https://doi.org/10.1056/nejmoa1916870.

64. Johnston SC, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med. 2018;379(3):215–25. https://doi.org/10.1056/nejmoa1800410.