Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 25s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Comparing the Efficacy of Ticagrelor and Clopidogrel in Patients with Acute Ischemic Stroke

Davood Kashipazha[1*], Shahram Rafie[1], Saeed Ghanbari[2], Maryam Alwanian[1]

[1]Department of Neurology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[2]Department of Biostatistics and Epidemiology, School of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[*]Corresponding Author
Davood Kashipazha,
Department of Neurology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Cite this paper as: Davood Kashipazha, Shahram Rafie, Saeed Ghanbari, Maryam Alwanian, (2025) Comparing the Efficacy of Ticagrelor and Clopidogrel in Patients with Acute Ischemic Stroke. *Journal of Neonatal Surgery*, 14 (25s), 296-304.

ABSTRACT

Introduction: This study compared the effects of using clopidogrel and ticagrelor for 90 days in reducing the risk of subsequent stroke or death and reducing related clinical symptoms, severe bleeding, and disability among patients with ischemic stroke.

Methods: The study was conducted as a randomized controlled clinical trial among patients with ischemic stroke referred to Golestan Hospital, Ahvaz. Two groups of patients were included and divided into each group in a 1:1 ratio using a simple random allocation method. The two groups received ticagrelor or clopidogrel plus aspirin within 24 hours after the onset of symptoms for 30 days. The trial's outcome was the combined risk of major ischemic events at 90 days. It was measured by the mRS (Modified Rankin Score) criterion and the incidence of recurrent stroke.

Results: In this study, 185 patients were studied in the ticagrelor + aspirin group and 187 in the clopidogrel + aspirin group. Comparing the two groups regarding the incidence of recurrent stroke at 90-day follow-up showed that the difference between the two groups was not significant, despite the higher percentage of recurrent stroke in the clopidogrel + aspirin group (9.1% vs. 7.0%) (P = 0.465).

Comparing the two groups regarding stroke outcome based on the mRS criterion at 90-day follow-up revealed that the mean mRS in the clopidogrel + aspirin group was significantly lower (1.87 ± 1.67 vs. 2.37 ± 1.79; P = 0.005).

Discussion and Conclusion: Based on the results, the two drug groups were not statistically significant regarding stroke outcomes. Since all cases of hemorrhagic transformation occurred in NIHSS ≥5, we should treat with caution in prescribing dual antiplatelet agents in these people.

Keywords: *Stroke, Clopidogrel, Ticagrelor.*

1. INTRODUCTION

Stroke is the most common disabling disorder of the brain and nervous system in adults (1). It is defined as a rapidly progressive focal deficit or generalized impairment of brain function with symptoms lasting 24 hours or more and not attributable to any cause other than vascular lesions (2). Ischemic stroke is the most common type of stroke and occurs when a blood vessel in the neck or brain is blocked, and the blood clot blocks blood flow to the brain. This blockage can be caused by a clot forming in a blood vessel in the brain or neck (thrombosis) or the clot moving from another part of the body, such as the heart, to the brain (embolism), or by a severe narrowing of an artery ending in the brain (stenosis) (3). The ischemic stroke risk varies from 3% to 15% in the 90 days following a mild ischemic stroke or a transient ischemic attack (TIA) (4). Antiplatelet drugs can be used to prevent recurrent stroke. Several trials have proven that aspirin reduces the risk of recurrent stroke by about 20% (5).

Clopidogrel is an antiplatelet drug that prevents blood clot formation by reducing the adhesion of platelets. Thus, it reduces the risk of heart attacks or strokes (6). Clopidogrel blocks platelet aggregation through the P2Y12 receptor pathway, a mechanism that is synergistic with aspirin in the inhibition of platelet aggregation. It has been proven that the combination

of these two drugs is more effective than aspirin alone in reducing the risk of ischemic events in patients with acute coronary syndromes (7). Ticagrelor is a new class of antiplatelet drugs (6). Clopidogrel requires hepatic conversion to its active form (8). It is a direct-acting antiplatelet agent that does not depend on metabolic activation and reversibly binds and inhibits the P2Y12 receptor on platelets (9).

A trial of ticagrelor alone in patients with acute ischemic stroke or TIA revealed no advantage over aspirin in preventing subsequent vascular events (stroke, myocardial infarction, or death) (6). Side effects of ticagrelor include bradyarrhythmia and dyspnea, in addition to bleeding (10). An exploratory analysis of the trial, which included a subgroup of patients who received aspirin within 7 days before randomization, reported that treatment with ticagrelor might reduce the risk of major vascular events (11). This result indicates that the effect of aspirin received before the trial may persist for several days after treatment and the combination of ticagrelor and aspirin may prevent subsequent strokes. A 30-day treatment period was considered appropriate for testing ticagrelor and aspirin in the prevention of subsequent stroke since the risk of subsequent stroke occurs predominantly in the first month after an acute ischemic stroke or TIA (11).

Johnston et al. (2018) published the results of a double-blind, randomized, placebo-controlled trial called Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT). The results revealed that in patients with minor ischemic stroke or high-risk TIA, those who received the combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major bleeding at 90 days compared with those who received aspirin alone (12). Patients with acute ischemic stroke are at high risk of recurrent stroke and cardiovascular events (4). The clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) trial showed that the combination of clopidogrel and aspirin was superior to aspirin alone in reducing the risk of stroke (17), but may increase the risk of non-cranial bleeding (13). Additionally, about 50% of patients with acute ischemic stroke have a history of atherosclerosis of the large intracranial artery (LAA) in Asia, and patients with intracranial stenosis and mild stroke (or high risk of transient ischemic attack) have a higher risk of recurrent stroke than patients without stroke (9). The genetic sub-study of the CHANCE trial indicated that patients carrying the cytochrome P450 (CYP) 2C19*2 and *3 loss-of-function alleles benefited more from aspirin alone than from dual antiplatelet therapy (14). Ticagrelor is metabolized primarily by the enzyme CYP3A4 and, unlike clopidogrel, does not involve CYP2C19 (15).

A genetic sub-study of the PLATO clinical trial revealed that ticagrelor was more effective than clopidogrel for acute coronary syndromes regardless of CYP2C19 genotype, but was associated with an increased risk of bleeding in patients with a history of stroke (16). The Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial showed a trend toward greater efficacy in reducing the risk of vascular events in the ticagrelor group compared with the aspirin group in an Asian population. However, there is limited information on the safety and efficacy of ticagrelor for the treatment of stroke compared with clopidogrel data in patients with acute stroke (6, 9, 17).

Hyperreactivity of platelets is defined as resistance or lack of response to antiplatelet agents. It is a known marker for recurrent ischemic events in patients with acute coronary syndromes or patients undergoing percutaneous coronary intervention (18). Several studies have proven the predictive value of hyperreactivity of platelets for ischemic events and bleeding after percutaneous coronary intervention or in patients with acute coronary syndromes. Multiple factors can be involved in the alteration of platelet function test results, thus characterizing the hyperreactivity status of platelets. Hyperreactivity of platelets is associated with poor cerebrovascular outcomes and may be of clinical value for the assessment of recurrent events in patients with stroke (19). This study compared the efficacy of using clopidogrel and ticagrelor for 90 days in reducing the risk of subsequent stroke or death and reducing associated clinical symptoms, major bleeding, and disability among patients with ischemic stroke.

2. MATERIALS AND METHODS

The statistical population of the present clinical t included patients referred to Golestan Hospital in Ahvaz with ischemic stroke from January 20 **23**to October 20**24**. The number of samples was calculated using the clinical trial calculation formula (20). The numbers to be used in the formula were obtained from the study by Wang et al. (21). A minimum of 184 people were calculated for each group using the MedCalc software with a power of 90% and an error of 5%. However, considering a 15% dropout, 212 patients were studied in each group. A convenience sampling method was used. Patients were included in the study if they were diagnosed with ischemic stroke or TIA based on the history, neurological examinations, and imaging findings by a specialist physician. The exclusion criteria for the study included the following items:

1. More than 24 hours have passed since the onset of symptoms
2. Thrombolytic therapy or thrombectomy
3. Intracranial hemorrhage
4. Vascular malformations
5. Contraindications to aspirin, clopidogrel, or ticagrelor
6. NIHSS above 12
7. Patient's unwillingness to continue the study
8. Contraindications to MRI

9. Acute coronary syndrome at the time of admission
10. Stroke or TIA with cardioembolic origin
11. Persistent dyspnea following ticagrelor intake
12. Persistent bradyarrhythmia following ticagrelor intake

Implementation method

This study was conducted after being approved by the Research Council of Ahvaz Jundishapur University of Medical Sciences and receiving the medical code of ethics of IR.AJUMS.REC.1402.551 from the relevant Research Deputy Department. All eligible subjects were selected based on the inclusion and exclusion criteria of the study. The subjects entered the study after that the researcher provided explanations to the patients about the objective and implementation of the project and obtained the subjects' informed and written consent. The provisions of the Declaration of Ethics in Helsinki Research and the principles of patient confidentiality were also observed in this study. Two groups of patients were considered and patients who were referred with ischemic stroke were divided into each group with a ratio of 1: 1 and by simple random allocation method. The two groups received ticagrelor or clopidogrel plus aspirin for 30 days from 24 hours after the onset of symptoms. After 30 days, aspirin alone was continued in both groups. First, patient data were recorded based on study variables in a pre-designed checklist. Some basic data required by patients were extracted from the " Stroke Registry of Khuzestan " (https://strok.ir).

The NIHSS criterion is defined as the sum of 15 individually assessed elements and varies from 0 to 42. Mild stroke is defined as a score of 1-4, moderate stroke as a score of 5-15, moderate to severe stroke as a score of 16-20, and severe stroke as a score of 21-42 (22). The intervention group (ticagrelor/aspirin) received aspirin (a loading dose of 300 mg as three 100 mg tablets on day 1, followed by 80 mg once daily) in the first 30 days along with ticagrelor (a loading dose of 180 mg as two 90 mg tablets on day 1, followed by 90 mg twice daily until day 30), and then aspirin alone. The control group received (clopidogrel/aspirin), aspirin (a loading dose of 300 mg as three 100 mg tablets on day 1, followed by 80 mg once daily) in the first 30 days along with clopidogrel (300 mg as a loading dose of four 75 mg tablets on day 1, followed by 75 mg once daily until day 30), and then aspirin alone. Patients were followed up in person and via phone on day 7 or at discharge, at the end of the first month, and at the end of the third month after ischemic stroke or TIA. The trial outcome was the composite risk of major ischemic events at 90 days, as measured by the Modified Rankin Score (mRS) and the incidence of recurrent stroke. (23).

3. RESULTS

Descriptive results

First, 424 patients with ischemic stroke, including 212 patients in each group, were enrolled in the study. At 90-day follow-up, 52 patients, including 27 patients in the ticagrelor + aspirin group and 25 patients in the clopidogrel + aspirin group, were excluded from the trial due to meeting the exclusion criteria. Finally, 372 patients with ischemic stroke, including 185 patients in the ticagrelor + aspirin group and 187 patients in the clopidogrel + aspirin group, were studied (Figure 1). Comparing the two groups regarding demographic variables, etiology, and stroke severity revealed a statistically significant difference only between the ethnicity of the patients in the two studied groups (P = 0.004), and no statistically significant relationship was observed for other variables (P>0.05) (Table 1).

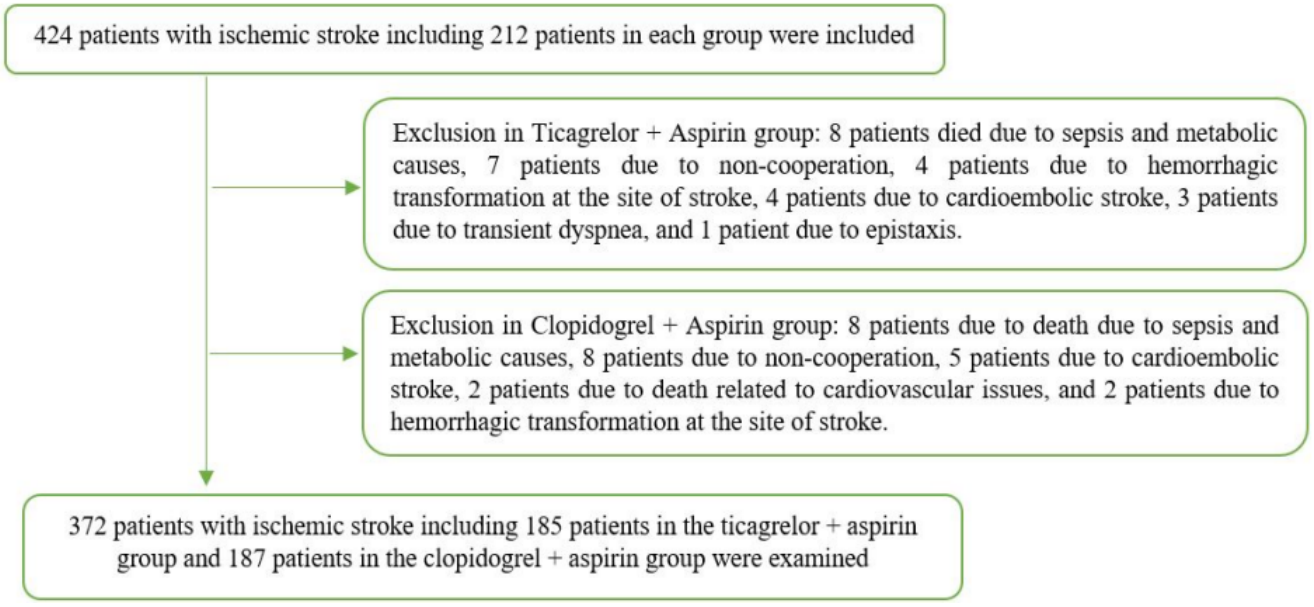

Figure 1. Determining the excluded and included patients in the trial

Table 1. Comparison of demographic information, etiology, and stroke severity between the two studied groups

Variables		ticagrelor + aspirin)n=185(	clopidogrel + aspirin (n=187)	P value
Gender	Female	86 (46.5)	84 (44.9)	0.762
	Male	99 (53.5)	103 (55.1)	
Ethnicity	Persian	56 (30.3)	84 (44.9)	0.004
	Arab	129 (69.7)	103 (55.1)	
Low activity/inactivity		144 (77.8)	156 (83.4)	0.173
Hypertension		92 (49.7)	91 (48.7)	0.837
Diabetes mellitus		52 (28.1)	59 (31.6)	0.468
Dyslipidemia		44 (23.8)	51 (27.3)	0.440
History of MI		0 (0.0)	2 (1.1)	0.158
History of CVA		11 (5.9)	16 (8.6)	0.332
History of TIA		32 (17.3)	31 (16.6)	0.853
History of smoking		50 (27.0)	41 (21.9)	0.252
Current smoking		28 (15.1)	42 (22.5)	0.071
Opioid use		6 (3.2)	6 (3.2)	0.985
Alcohol consumption		2 (1.1)	1 (0.5)	0.556
Etiology of stroke	LAA	106 (50.0)	98 (52.4)	0.802
	Small vessel disease	66 (35.7)	67 (35.8)	
	Unknown cause	18 (9.7)	22 (11.8)	
CVA/TIA	CVA	167 (90.3)	163 (87.2)	0.344
	TIA	18 (9.7)	24 (12.8)	
		SD ±Mean		
Age		62.29 ±12.01	61.09 ±12.19	0.298
Age group	>62 years	79 (42.7)	88 (47.1)	0.398
	<62 years	106 (57.3)	99 (52.9)	
BMI (Kg/m^2)		25.44 ±3.02	25.35 ±2.94	0.906
hypertension	Systolic	133.04 ±16.15	130.94 ±15.66	0.194
	Diastolic	73.91 ±11.87	73.45 ±12.28	0.628
NIHSS at admission		4.88 ±2.76	4.37 ±2.70	0.095
Stroke severity at admission	Mild	88 (47.6)	101 (54.0)	0.214
	Moderate	114 (53)	104 (49)	
NIHSS at discharge		4.28 ±2.72	4.10 ±2.67	0.634
Stroke severity at discharge	Mild	101 (54.6)	107 (57.2)	0.610
	Moderate	84 (45.4)	80 (42.8)	

Independent t-test and Chi-square

Analytical results

Comparing the two groups regarding the incidence of recurrent stroke at 90-day follow-up did not show a significant difference between the two groups despite the higher percentage of recurrent stroke in the clopidogrel + aspirin group (9.1% vs. 7.0%) (P = 0.465) (Figure 1).

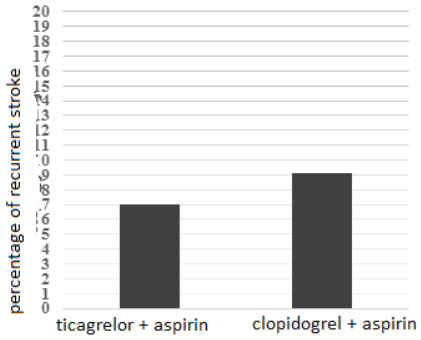

Figure 2. Comparison of the two groups regarding the incidence of recurrent stroke at 90-day follow-up

Comparing the two groups regarding stroke outcome based on the mRS criterion at 90-day follow-up revealed that the mean mRS in the clopidogrel + aspirin group was significantly lower (1.87 ± 1.67 vs. 2.37 ± 1.79; P = 0.005), meaning that stroke in patients taking clopidogrel + aspirin was significantly associated with a better outcome than in patients taking ticagrelor + aspirin (Figure 2).

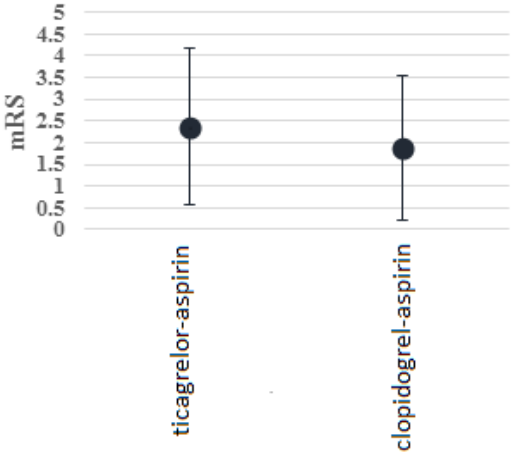

Figure 3. Comparison of the two groups regarding stroke outcome based on the mRS criterion at 90-day follow-up

Comparing the primary outcomes of stroke with the etiology of large vessel atherosclerosis in the ticagrelor-aspirin group revealed that the number/percentage of recurrent strokes (5%) was 8, the number/percentage of deaths (1.8%) was 2, the number/percentage of hemorrhagic transformation (1.8%) was 2. Additionally, in the clopidogrel-aspirin group, the number/percentage of recurrent stroke (12.2%) was 12 (P = 0.314). Generally, the difference in the primary outcomes in the two groups was not statistically significant (Table 2).

Table 2. Comparison of the primary outcomes in stroke with the etiology of LAA in the ticagrelor-aspirin and clopidogrel-aspirin groups

Study variable	clopidogrel-aspirin group	ticagrelor-aspirin group	P Value
Number/percentage of patients with LAA etiology	98 (52.4)	106 (50.0)	P > 0.05
Number/percentage of recurrent stroke	12 (12.2)	8 (5.0)	0.314
Number/percentage of death	0	2 (1.8)	P > 0.05
Number/percentage of hemorrhagic transformation	0	2 (1.8)	P > 0.05

Independent t-test

Comparing the primary outcomes in patients with NIHSS <5 in the ticagrelor-aspirin group revealed that the number/percentage of recurrent stroke (14.7%) was 13 (P =0.576) and the number/percentage of deaths and the number/percentage of hemorrhagic transformation were 0. In the clopidogrel-aspirin group, the number/percentage of recurrent stroke (8.9%) was 9 and the number/percentage of death and hemorrhagic transformation were 0. Generally, the difference in primary outcomes between the two groups was not statistically significant (Table 3). Comparing the primary outcomes in patients with NIHSS ≥5 in the ticagrelor-aspirin group revealed that the number/percentage of recurrent strokes (1.7%) was 2, the number/percentage of deaths (7.0%) was 8, and the number/percentage of hemorrhagic transformation (3.5%) was 4. In the clopidogrel-aspirin group, the number/percentage of recurrent stroke (6.7%) was 7 (P=0.068), the number/percentage of death (9.6%) was 10, and the number/percentage of hemorrhagic transformation (1.9%) was 2. Overall, the difference in primary outcomes between the two groups was not statistically significant (Table 3).

Table 3- Comparison of primary outcomes in patients with NIHSS<5 and NIHSS≥5 in the ticagrelor-aspirin and clopidogrel-aspirin groups

	Study variable	clopidogrel-aspirin group	ticagrelor-aspirin group	P Value
NIHSS <5	Number/percentage of patients	101 (54.0)	88 (47.6)	P > 0.05
	Number/percentage of recurrent stroke	9 (8.9)	13 (14.7)	0.576
	Number/percentage of death	0	0	P > 0.05
	Number/percentage of hemorrhagic transformation	0	0	P > 0.05
NIHSS ≥5	Number/percentage of patients	104 (49)	114 (53)	P > 0.05
	Number/percentage of recurrent stroke	7 (6.7)	2 (1.7)	0.068
	Number/percentage of death	10 (9.6)	8 (7.0)	P > 0.05
	Number/percentage of hemorrhagic transformation	2 (1.9)	4 (3.5)	P > 0.05

Independent t-test

Comparing the two groups regarding the occurrence of recurrent stroke and stroke outcome based on the mRS criterion in the 90-day follow-up by gender revealed no significant difference in the occurrence of recurrent stroke and stroke outcome between the two groups in males (P > 0.05). However, in females, the mean mRS in the clopidogrel + aspirin group was significantly lower (P = 0.539) despite the lack of significant difference in the occurrence of recurrent stroke between the two groups (1.81 ± 1.69 vs. 2.50 ± 1.70; P = 0.008). It means that stroke in women taking clopidogrel + aspirin was significantly associated with a better outcome than in women taking ticagrelor + aspirin (Table 4). Comparing the two groups regarding the occurrence of recurrent stroke and stroke outcomes based on the mRS criterion in the 90-day follow-up by age group revealed no significant difference between the two groups in patients aged 62 years or older regarding the occurrence of recurrent stroke and stroke outcomes (P > 0.05). However, in patients younger than 62 years, the mean mRS in the clopidogrel + aspirin group was significantly lower (1.56 ± 1.64 vs. 2.22 ± 1.79; P = 0.009) despite the lack of a significant difference in the occurrence of recurrent stroke between the two groups (P = 0.610). This means that stroke in patients younger than 62 years using clopidogrel + aspirin was significantly associated with a better outcome than in patients using ticagrelor + aspirin (Table 4).

Table 4. Comparison of the two groups regarding the occurrence of recurrent stroke and stroke outcome based on gender and age group

Gender	Study variable		ticagrelor + aspirin	clopidogrel + aspirin	P value
Males	Recurrent stroke	Yes	7 (7.1)	13 (12.6)	0.187
		No	92 (0.93)	90 (0.87)	
	Stroke outcome (mRS)		2.26 ±1.86	1.91 ±1.66	0.183

Females	Recurrent stroke	Yes	6 (7.0)	4 (4.8)	0.539
		No	80 (0.93)	80 (0.95)	
	Stroke outcome (mRS)		2.50 ±1.70	1.81 ±1.69	0.008
Age group	Study variable		ticagrelor + aspirin	clopidogrel + aspirin	P value
> 62 years	Recurrent stroke	Yes	5 (6.3)	4 (4.5)	0.610
		No	74 (0.94)	84 (0.96)	
	Stroke outcome (mRS)		2.22 ±1.79	1.56 ±1.64	0.009
≤62 years	Recurrent stroke	Yes	8 (7.5)	13 (13.1)	0.188
		No	98 (0.925)	86 (0.869)	
	Stroke outcome (mRS)		2.49 ±1.79	2.14 ±1.66	0.162

Independent t-test and Chi-square

4. DISCUSSION

This study compared the efficacy of clopidogrel and ticagrelor for 90 days in reducing the risk of subsequent stroke or death and reducing associated clinical symptoms, major bleeding, and disability among patients with ischemic stroke. In this study, 372 patients with ischemic stroke, including 185 patients in the ticagrelor + aspirin group and 187 patients in the clopidogrel + aspirin group, were studied. Comparing the two groups regarding the incidence of recurrent stroke at 90-day follow-up did not show a significant difference between the two groups (P = 0.465), despite the higher percentage of recurrent stroke in the clopidogrel + aspirin group (9.1% vs. 7.0%).

Comparing the two groups regarding stroke outcome based on the mRS criterion at 90-day follow-up showed that the mean mRS in the clopidogrel + aspirin group was significantly lower (1.87 ± 1.67 vs. 2.37 ± 1.79; P = 0.005). This means that stroke in patients taking clopidogrel + aspirin was significantly associated with a better outcome than in patients taking ticagrelor + aspirin. The differences were not statistically significant despite higher rates of major and minor bleeding and dyspnea, and lower rates of cardiovascular death in the ticagrelor-aspirin group compared with the clopidogrel-aspirin group.

Previous studies have yielded conflicting results regarding the effectiveness of ticagrelor on stroke outcomes. For example, a study by Johnston et al. (2020) showed that among patients with mild to moderate acute noncardiac embolic ischemic stroke (NIHSS score ≤5) or TIA who did not undergo intravenous or endovascular thrombolysis, the risk of stroke or death within 30 days with ticagrelor-aspirin was lower than with aspirin alone. However, the incidence of disability was not significantly different between the two groups (24). The trial by Johnston et al. (2016) revealed that ticagrelor was not superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days (25).

Wang et al. compared ticagrelor and clopidogrel in 26 medical centers in China from August 2015 to March 2017 and showed no difference between the ticagrelor/aspirin and clopidogrel/aspirin groups in the rates of major or minor bleeding events (21). Despite the similarity in the methodology of the two studies, in our study, females in the age group under 62 years of age taking clopidogrel and aspirin had a significantly better outcome than taking ticagrelor and aspirin. The difference in results can be attributed to the differences in the characteristics of the patients studied such as ethnicity and genetics and differences in the initial mRS of the patients since genetic differences can affect metabolism, and thus the effectiveness of the drug in the body given the different metabolic pathways of the two drugs.

Comparing the two groups regarding the occurrence of recurrent stroke and stroke outcomes based on the mRS criterion in the 90-day follow-up by gender showed no significant difference between the two groups in males regarding the occurrence of recurrent stroke and stroke outcomes (P > 0.05). However, the mean mRS in the clopidogrel + aspirin group was significantly lower (1.81 ± 1.69 vs. 2.50 ± 1.70; P = 0.008 in females, despite the lack of significant difference between the two groups in the occurrence of recurrent stroke (P = 0.539). This means that stroke in females taking clopidogrel + aspirin was significantly associated with better outcomes than in females taking ticagrelor r+ aspirin.

Additionally, comparing the two groups regarding the occurrence of recurrent stroke and stroke outcomes based on the mRS criterion in the 90-day follow-up by age group showed no significant difference between the two groups in patients aged 62 years or older regarding the occurrence of recurrent stroke and stroke outcomes (P > 0.05). However, in female patients younger than 62 years, the mean mRS in the clopidogrel + aspirin group was significantly lower (1.56 ± 1.64 vs. 2.22 ± 1.79; P = 0.009) despite the lack of significant difference between the two groups in the occurrence of recurrent stroke (P = 0.610). This means that stroke in female patients younger than 62 years using clopidogrel + aspirin was significantly associated with a better outcome than in patients using ticagrelor + aspirin. Thus, the use of clopidogrel plus aspirin in females and patients under 62 years of age is associated with a better outcome regarding 3-month mRS than the use of ticagrelor and aspirin. Comparing the primary outcomes in stroke with large vessel atherosclerosis etiology in the ticagrelor-aspirin group showed that the number/percentage of recurrent strokes (5%) was 8, the number/percentage of deaths (1.8%) was 2, and the number/percentage of hemorrhagic transformation, (1.8%) was 2. In the clopidogrel-aspirin group, the number/percentage of recurrent strokes (12.2%) was 12 (P = 0.314). Generally, the difference in primary outcomes between the two groups was

not statistically significant. Comparing the primary outcomes in patients with NIHSS <5 in the ticagrelor-aspirin group showed that the number/percentage of recurrent stroke (14.7%) was 13 (P = 0.576) and the number/percentage of deaths and the number/percentage of hemorrhagic transformation were 0. In the clopidogrel-aspirin group, the number/percentage of recurrent stroke (8.9%) was 9 and the number/percentage of death and hemorrhagic transformation were 0. Comparing the primary outcomes in patients with NIHSS ≥5 in the ticagrelor-aspirin group showed that the number/percentage of recurrent strokes (1.7%) was 2, the number/percentage of deaths (0.7%) was 8, and the number/percentage of hemorrhagic transformation (3.5%) was 4. In the clopidogrel-aspirin group, the number/percentage of recurrent stroke (6.7%) was 7 (P = 0.068), the number/percentage of death (6.9%) was 10, and the number/percentage of hemorrhagic transformation (1.9%) was 2. Generally, the difference in primary outcomes between the two groups was not statistically significant.

5. CONCLUSION

The results of comparing two drug groups regarding primary and secondary stroke outcomes did not show a significant difference. It is recommended to conduct a study in larger populations and eliminate confounding factors. Given that all cases of hemorrhagic transformation occurred in NIHSS ≥5, we should treat with caution in prescribing dual antiplatelet in these individuals. In addition, conducting review studies and meta-analyses, while integrating the results of different studies, will help to reach a consensus regarding the effectiveness of drug combinations and the selection of the gold standard of treatment.

REFERENCES

1. Fiuji H, Namayandeh S, Erfani M. Epidemiologic study of the main risk factors for one-year ischemic stroke and surivial in patients admitted to the Neurology Department of Ghayim Hospital in Mashhad, Iran, 2015. Tolooebehdasht. 2020;19(2):33-42**.**
2. Schouten EA, Schiemanck SK, Brand N, Post MW. Long-term deficits in episodic memory after ischemic stroke: evaluation and prediction of verbal and visual memory performance based on lesion characteristics. Journal of stroke and cerebrovascular diseases. 2009**;**18(2):128-38.
3. Randolph SA. Ischemic stroke. Workplace health & safety. 2016;64(9):444.
4. Amarenco P, Lavallée PC, Labreuche J, Albers GW, Bornstein NM, Canhão P, et al. One-year risk of stroke after transient ischemic attack or minor stroke. New England Journal of Medicine. 2016;374(16):1533-42**.**
5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, 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 Association. Stroke. 2019;50(12): e344-e418
6. Johnston S, Amarenco P, Albers G, Denison H, Easton J, Evans S, et al. SOCRATES Steering Committee and Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med. 2016;375(1):35-43**.**
7. Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. The American journal of cardiology. 2008;101(7):960-6**.**
8. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. Journal of the American College of Cardiology. 2007;50(19):1852-6**.**
9. Wang Y, Minematsu K, Wong KSL, Amarenco P, Albers GW, Denison H, et al. Ticagrelor in acute stroke or transient ischemic attack in Asian patients: from the SOCRATES trial (acute stroke or transient ischemic attack treated with aspirin or ticagrelor and patient outcomes). Stroke. 2017;48(1):167-73**.**
10. Cesarini, D.; Muraca, I.; Berteotti, M.; Gori, A.M.; Sorrentino, A.; Bertelli, A.; Marcucci, R.; Valenti, R. Pathophysiological and Molecular Basis of the Side Effects of Ticagrelor: Lessons from a Case Report. Int. J. Mol. Sci. 2023, 24, 10844. https://doi.org/10.3390/ ijms241310844
11. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. New England Journal of Medicine. 2020;383(3):207-17**.**
12. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. New England Journal of Medicine. 2018;379(3):215-25**.**
13. Wang D, Gui L, Dong Y, Li H, Li S, Zheng H, et al. Dual antiplatelet therapy may increase the risk of non-intracranial haemorrhage in patients with minor strokes: a subgroup analysis of the CHANCE trial. Stroke and Vascular Neurology. 2016;1.(2)
14. Liu L, Wong KSL, Leng X, Pu Y, Wang Y, Jing J, et al. Dual antiplatelet therapy in stroke and ICAS: subgroup analysis of CHANCE. Neurology. 2015;85(13):1154-62**.**

15. Brilakis ES, Patel VG, Banerjee S. Medical management after coronary stent implantation: a review. Jama. 2013;310(2):189-98.
16. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. The Lancet. 2010;376(9749):1320-8.
17. Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, et al. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. The Lancet Neurology. 2017;16(4):301-10.
18. Cuisset T, Frere C ,Quilici J, Barbou F, Morange P, Hovasse T, et al. High post-treatment platelet reactivity identified low-responders to dual antiplatelet therapy at increased risk of recurrent cardiovascular events after stenting for acute coronary syndrome. Journal of Thrombosis and Haemostasis. 2006;4(3):542-9.
19. Fiolaki A, Katsanos AH, Kyritsis AP, Papadaki S, Kosmidou M, Moschonas IC, et al .High on treatment platelet reactivity to aspirin and clopidogrel in ischemic stroke: A systematic review and meta-analysis. Journal of the neurological sciences. 2017; 376:112-6.
20. Gupta K, Attri J, Singh A, Kaur H, Kaur G. Basic concepts for sample size calculation: critical step for any clinical trials! Saudi journal of anaesthesia. 2016;10(3):328.
21. Wang Y, Chen W, Lin Y, Meng X, Chen G, Wang Z, et al. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. bmj. 2019;365.
22. Samuel OW, Fang P, Chen S, Geng Y, Li G. Activity recognition based on pattern recognition of myoelectric signals for rehabilitation. In: Khan SU, Zomaya AY, Abbas A, editors. Handbook of large-scale distributed computing in smart healthcare. Basel: Springer International Publishing AG; 2017.
23. Zihni E, McGarry BL, Kelleher JD. Moving Toward Explainable Decisions of Artificial Intelligence Models for the Prediction of Functional Outcomes of Ischemic Stroke Patients. In: Linwood SL, editor. Digital Health [Internet]. Brisbane (AU): Exon Publications; 2022 Apr 29.
24. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. New England Journal of Medicine. 2020;383(3):207-17.
25. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al .Ticagrelor versus aspirin in acute stroke or transient ischemic attack. New England Journal of Medicine. 2016;375(1):35-43.