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Efficacy and Safety of Prasugrel vs Clopidogrel in Thrombotic Stroke Patients With Risk Factors for Ischemic Stroke Recurrence: A Double-blind, Phase III Study (PRASTRO-III)

Takanari Kitazono[1], Masahiro Kamouchi[2], Yuji Matsumaru[3], Masato Nakamura[4], Kazuo Umemura[5], Hajime Matsuo[6], Nobuyuki Koyama[6], Junko Tsutsumi[6] and Kazumi Kimura[7]

[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[2]Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[3]Division of Stroke Prevention and Treatment, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[4]Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan
[5]Department of Pharmacology, Hamamatsu University School of Medicine, Shizuoka, Japan
[6]Daiichi Sankyo Co., Ltd., Tokyo, Japan
[7]Department of Neurological Science, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Aim: To examine the efficacy and safety of prasugrel vs clopidogrel in thrombotic stroke patients at risk of ischemic stroke.

Methods: This multicenter, active-controlled, randomized, double-blind, double-dummy, parallel group study enrolled thrombotic stroke patients aged ≥ 50 years at risk of ischemic stroke. Patients received prasugrel (3.75 mg/day) or clopidogrel (75 or 50 mg/day) for 24–48 weeks; other antiplatelet drugs were prohibited. The primary efficacy endpoint was the composite incidence of ischemic stroke, myocardial infarction (MI), and death from other vascular causes from the start to 1 day after treatment completion or discontinuation. Secondary efficacy endpoints included the incidences of ischemic stroke, MI, death from other vascular causes, ischemic stroke and transient ischemic attack, and stroke. Safety endpoints included bleeding events and adverse events (AEs).

Results: In the prasugrel (N=118) and clopidogrel (N=112; all received 75 mg) groups, the primary efficacy endpoint composite incidence (95% confidence interval) was 6.8% (3.0%–12.9%) and 7.1% (3.1%–13.6%), respectively. The risk ratio (prasugrel/clopidogrel) was 0.949 (0.369–2.443). Secondary efficacy endpoints followed a similar trend. The combined incidences of life-threatening, major, and clinically relevant bleeding were 5.0% and 3.5% in the prasugrel and clopidogrel groups, respectively. The incidences of all bleeding events and AEs were 19.2% and 24.6% and 76.7% and 82.5% in the prasugrel and clopidogrel groups, respectively. No serious AEs were causally related to prasugrel.

Conclusions: We observed a risk reduction of 5% with prasugrel vs clopidogrel, indicating comparable efficacy. There were no major safety issues for prasugrel.

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Key words: Thrombotic stroke, Clopidogrel, Phase III, Prasugrel

Abbreviations: AEs, adverse events; ASO, arteriosclerosis obliterans; CI, confidence interval; EM, extensive metabolizer; FAS, full analysis set; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme-A; IM, intermediate metabolizer; MI, myocardial infarction; PM, poor metabolizer; PRU, $P2Y_{12}$ reaction unit; SD, standard deviation; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment

Clinical Trial Registration: JapicCTI-184141

Address for correspondence: Takanari Kitazono, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka City, 812-8582 Japan E-mail: kitazono.takanari.362@m.kyushu-u.ac.jp

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Introduction

For the prevention of recurrence of non-cardioembolic stroke, the Japanese Guidelines for the Management of Stroke recommend cilostazol, clopidogrel, and aspirin as antiplatelet therapy[1]. Of these, clopidogrel is the most frequently used worldwide.

Prasugrel is an adenosine diphosphate receptor antagonist with a thienopyridine structure that exhibits a faster, stronger, and more stable antiplatelet action than that of clopidogrel[2]. Prasugrel has been approved in Europe, the US, and Japan for the treatment of patients with heart disease who have undergone percutaneous coronary intervention[3-5]. In the field of cerebrovascular medicine, the efficacy and safety of prasugrel have been demonstrated in two multicenter, double-blind, comparative studies (PRASTRO-I, PRASTRO-II) conducted in patients with non-cardioembolic stroke in Japan[6, 7].

Data from the SOCRATES and CHANCE studies have shown that patients with large-artery atherosclerosis due to intracranial or extracranial arterial stenosis benefit from strong antiplatelet therapy in the acute phase[8, 9]. In addition, a sub-analysis of the PRASTRO-I study (by stroke subtype) showed that prasugrel, which has a strong antiplatelet effect, was as effective as clopidogrel in patients with large-artery atherosclerosis and small-vessel occlusion[10]. However, expected results were not obtained in patients with stroke of undetermined etiology; in this population, the possibility of embolic stroke has been suggested in recent years[10]. In patients with thrombotic stroke, which is thought to be caused by platelet-derived thrombus, the composite incidence of ischemic stroke (fatal and non-fatal), myocardial infarction (MI; fatal and non-fatal), and death from other vascular causes was 3.5% in the prasugrel group and 4.3% in the clopidogrel group[6]. The hazard ratio (95% confidence interval [CI]) was 0.81 (0.53–1.22), indicating a 19% risk reduction with prasugrel administration[6].

Aim

The objective of the present study was to examine the efficacy and safety of prasugrel vs clopidogrel in thrombotic stroke patients with risk factors for ischemic stroke recurrence, using the composite incidence of ischemic stroke, MI, and death from other vascular causes as an index of efficacy and the incidence of bleeding events as an index of safety.

Methods

Study Design

This was a multicenter, active-controlled, randomized, double-blind, double-dummy, parallel group comparison study (PRASTRO-III) conducted from October 2018 to April 2020 in 43 institutions in Japan. The list of participating institutions is included in the Supplementary Materials. The trial was registered with the Japan Pharmaceutical Information Center (JapicCTI-184141).

For this study, thrombotic stroke was defined as large-artery atherosclerosis or small-vessel occlusion according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[11]. Thrombotic stroke patients with risk factors for ischemic stroke were enrolled via a web-based interactive response technology system, received treatment for 24–48 weeks, and were then followed up for 2 weeks after the completion or discontinuation of the study treatment.

Antiplatelet drugs, anticoagulants, thrombolytic drugs, and acidic nonsteroidal anti-inflammatory drugs were prohibited from the start of the study treatment to study completion or discontinuation of the study treatment. Participation in another clinical study was prohibited from 12 weeks before informed consent to the last day of the follow-up period.

Statement of Ethics

The study fully adheres to the ethical principles of the Declaration of Helsinki as well as GCP guidelines. The study protocol was approved by the Institutional Review Board/Ethics Committee of each participating institution. All study participants provided written informed consent.

Randomization and Blinding

The randomization schedule was prepared by an independent statistician and patients, investigators, and the sponsor were blinded to treatment allocation. Patients were assigned in a 1:1 ratio to prasugrel (3.75 mg/day orally) or clopidogrel (75 mg/day or 50 mg/day orally) using a permuted block technique with age (≥ 75 years, <75 years) and history of stroke before the last episode of attack (present, absent) as stratification factors. The variation in the dosage of clopidogrel was due to the fact that 75 mg is the usual dose in Japan, and 50 mg is used for elderly and underweight patients.

Patients

The main inclusion criteria were patients aged ≥ 50 years at the time of consent, with ischemic

lesions confirmed by MRI and corresponding with the observed neurological symptoms, whose ischemic stroke type corresponded to either large-artery atherosclerosis or small-vessel occlusion according to the TOAST classification and who had risk factors including hypertension, diabetes, chronic kidney disease, dyslipidemia, or a history of ischemic stroke. These were incorporated into the inclusion criteria based on subgroup analyses of the PRASTRO-I trial, which confirmed a favorable reduction in ischemic cerebrovascular and cardiovascular events in patients with these risk factors. Full inclusion and exclusion criteria are provided in the Supplemental Methods.

Efficacy

The primary efficacy endpoint was the composite incidence of ischemic stroke, MI, and death from other vascular causes observed during the period from the start of administration to 1 day after completion of treatment or discontinuation. The secondary efficacy endpoints were the incidences of each of the following: ischemic stroke, MI, death from other vascular causes, ischemic stroke and transient ischemic attack (TIA), and stroke from (1) the start of administration to 1 day after completion of treatment or discontinuation and from (2) the start of administration to the end of the follow-up period or discontinuation. Event definitions are provided in the Supplemental Methods. All efficacy events were evaluated by the independent Efficacy Event Evaluation Committee in a blinded manner.

Safety

The primary safety endpoint was the incidence of bleeding events, comprising life-threatening bleeding, major bleeding, and clinically relevant bleeding observed during the period from the start of administration until 14 days after completion of treatment or discontinuation. Bleeding event definitions are given in the Supplemental Methods. All bleeding events were evaluated by the independent Bleeding Event Evaluation Committee in a blinded manner. We also evaluated the incidence of adverse events (AEs) during the study.

Additional Outcomes

The pharmacodynamics of prasugrel vs clopidogrel were evaluated by measuring $P2Y_{12}$ reaction unit (PRU) values.

Subjects who provided separate informed consent for participation in this analysis were eligible for genetic polymorphism analysis of CYP2C19. The incidence of efficacy events from the start of administration to 1 day after completion of treatment or discontinuation according to CYP genetic polymorphism was evaluated in each group. Further details of the genetic polymorphism analysis are provided in the Supplemental Methods.

Statistical Analysis

The target number of cases was set at 250 (125 subjects per group). A full description of the sample size calculations and definitions of the analysis sets are provided in the Supplemental Methods. For the efficacy and safety endpoints, we calculated the incidence of events and 95% CIs for each treatment group, and the risk ratio and 95% CIs of prasugrel vs clopidogrel. The cumulative incidence of events was estimated and plotted for each treatment group using the Kaplan–Meier method. All statistical analyses were performed using SAS® Version 9.3 or higher (SAS Institute Inc., Cary, NC, USA).

Results

Patients

The disposition of patients is shown in **Fig. 1**. Of 235 patients randomly assigned to treatment, all except one, who had not taken the study drug, transitioned to the treatment phase. All patients received the 75 mg clopidogrel dosage; none received 50 mg. The prasugrel and clopidogrel groups included 120 and 114 patients, respectively. Two patients in each group dropped out from the full analysis set owing to violation of the inclusion criteria.

There were no clinically meaningful differences in the baseline characteristics of patients in both groups **(Table 1)**. The mean age of patients was approximately 70 years and 71% of patients were male.

Primary Efficacy Endpoint

The composite incidence of ischemic stroke, MI, and death from other vascular causes was 6.8% (8/118) (95% CI 3.0–12.9) in the prasugrel group and 7.1% (8/112) (95% CI 3.1–13.6) in the clopidogrel group, with a risk ratio (prasugrel/clopidogrel) of 0.949 (95% CI 0.369–2.443) **(Table 2)**. A Kaplan–Meier plot of the cumulative incidence of the primary efficacy endpoint is shown in **Fig. 2a**.

Secondary Efficacy Endpoints

The incidence of ischemic stroke, MI, and death from other vascular causes from the start of administration to the end of the follow-up period was similar to that of the primary efficacy endpoint **(Supplementary Table 1)**. The incidences of each secondary efficacy event from the start of

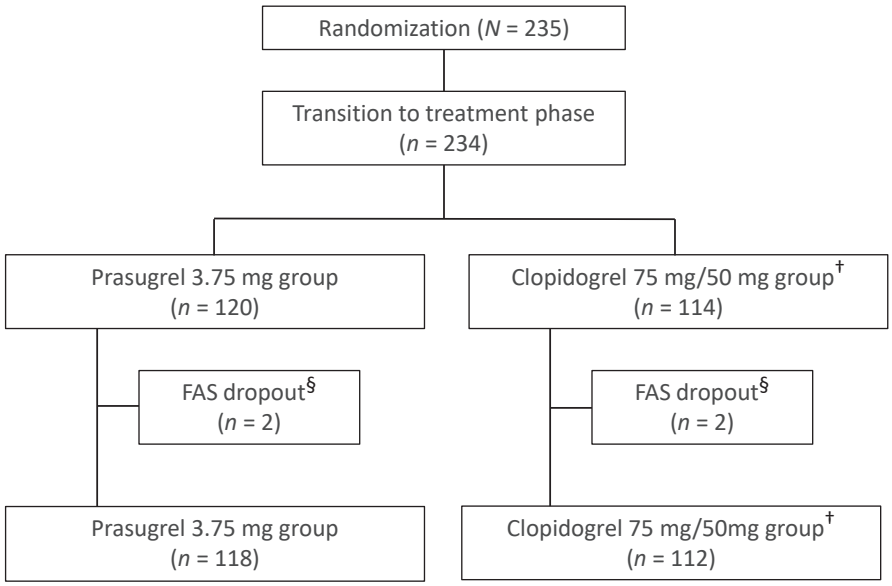

Fig. 1. Patient disposition

§Reason for FAS dropout: violation of inclusion criteria.
†All patients received the 75 mg/day clopidogrel dosage; none received 50 mg/day.
Abbreviation: FAS, full analysis set.

administration to 1 day after completion of treatment or discontinuation are shown in **Table 2**. A Kaplan–Meier plot of the cumulative incidence of ischemic cerebrovascular events (a composite of ischemic stroke and TIA) is shown in **Fig. 2b**.

Safety

The incidence of bleeding events is shown in **Table 2**. The combined incidence of life-threatening, major, and clinically relevant bleeding was 5.0% in the prasugrel group and 3.5% in the clopidogrel group. One case of major bleeding was reported in the prasugrel group (retinal tear), but no causal relationship with the study drug was observed. All clinically relevant bleeding events in the prasugrel group were mild and one event in the clopidogrel group was considered serious. None of the bleeding events developed into life-threatening bleeding. The incidence of all bleeding events was 19.2% in the prasugrel group and 24.6% in the clopidogrel group.

The incidence of AEs was 76.7% and 82.5% in the prasugrel and clopidogrel groups, respectively **(Supplementary Table 2)**. There were no serious AEs with a causal relationship to prasugrel.

Other Outcomes

The PRU level was consistently low numerically in the prasugrel group at 4 and 24 weeks **(Supplementary Fig. 1)**. **Supplementary Table 3** shows the incidence of efficacy events from the start of administration to 1 day after completion of treatment or discontinuation according to CYP genetic polymorphism.

Discussion

The PRASTRO-III study was conducted in patients with thrombotic stroke who had a high risk of ischemic stroke recurrence. Based on the results of the PRASTRO-I study, we expected that prasugrel would show a risk ratio of less than 1 among the high-risk ischemic stroke patients in the PRASTRO-III study. Indeed, our results showed that, similar to the PRASTRO-I and PRASTRO-II studies, the risk ratio was less than 1. This suggests that in high-risk patients, the event rate of ischemic stroke recurrence is likely to be lower with prasugrel than with clopidogrel. Overall, since the number of cases in this study was small, it is necessary to consider these results together with those of PRASTRO-I and PRASTRO-II[6, 7, 10].

Similarly, in patients with large-artery atherosclerosis and small-artery occlusion in the sub-analysis of the PRASTRO-I study[10], the incidence of the composite primary endpoint tended to be lower in the prasugrel group compared with the clopidogrel group. For large-artery atherosclerosis, the incidence was 3.8% (21 of 553 patients) versus 4.8% (26 of 546 patients) for the prasugrel versus clopidogrel groups,

Table 1. Patient demographic and clinical characteristics

		Prasugrel 3.75 mg *N*=118	Clopidogrel 75/50 mg *N*=112
Age (years)	Mean ± SD	70.5 ± 9.38	70.0 ± 9.50
	Median (min, max)	70.0 (50, 91)	71.0 (50, 89)
	≥ 75 years	41 (34.7)	39 (34.8)
Sex	Male	84 (71.2)	79 (70.5)
	Female	34 (28.8)	33 (29.5)
Weight (kg)	Mean ± SD	62.81 ± 10.957	64.35 ± 11.360
	Median (min, max)	62.25 (35.8, 86.8)	64.20 (40.1, 99.4)
	≤ 50 kg	16 (13.6)	11 (9.8)
Days from the last stroke until the start of treatment	≥ 7 days < 4 weeks	105 (89.0)	102 (91.1)
	≥ 4 weeks < 8 weeks	12 (10.2)	10 (8.9)
	≥ 8 weeks < 12 weeks	0 (0.0)	0 (0.0)
	≥ 12 weeks	0 (0.0)	0 (0.0)
	Missing	1 (0.8)	0 (0.0)
Type of last stroke	Atherosclerosis of large blood vessel	65 (55.1)	73 (65.2)
	Occlusion of small blood vessel	53 (44.9)	39 (34.8)
Risk factors	Hypertension	89 (75.4)	75 (67.0)
	Diabetes	38 (32.2)	41 (36.6)
	Chronic kidney disease	7 (5.9)	11 (9.8)
	Dyslipidemia	5 (4.2)	3 (2.7)
	Two or more risk factors	7 (5.9)	13 (11.6)
	History of ischemic stroke	21 (17.8)	19 (17.0)
Modified Rankin Scale	Grade 0	14 (11.9)	18 (16.1)
	Grade 1	27 (22.9)	36 (32.1)
	Grade 2	46 (39.0)	41 (36.6)
	Grade 3	24 (20.3)	6 (5.4)
	Grade 4	7 (5.9)	11 (9.8)
	Grade 5	0 (0.0)	0 (0.0)
History of arteriosclerotic disease	No	90 (76.3)	86 (76.8)
	Yes	28 (23.7)	26 (23.2)
	History of ischemic stroke	21 (17.8)	19 (17.0)
	History of TIA	4 (3.4)	5 (4.5)
	History of MI	5 (4.2)	2 (1.8)
	History of unstable angina	1 (0.8)	1 (0.9)
	History of chronic ASO	2 (1.7)	1 (0.9)
Complications	Hypertension	103 (87.3)	100 (89.3)
	Dyslipidemia	55 (46.6)	58 (51.8)
	Chronic kidney disease	8 (6.8)	14 (12.5)
	Diabetes	47 (39.8)	51 (45.5)
Concomitant drugs	Proton-pump inhibitor	72 (61.0)	82 (73.2)
	Ca antagonist	51 (43.2)	54 (48.2)
	HMG-CoA reductase inhibitor	83 (70.3)	79 (70.5)
	Angiotensin II receptor antagonist	40 (33.9)	44 (39.3)
	Insulin	7 (5.9)	9 (8.0)
Smoking habits	Non-smoker	44 (37.3)	37 (33.0)
	Former smoker	48 (40.7)	52 (46.4)
	Smoker	26 (22.0)	23 (20.5)
CYP2C19 phenotype	EM	37 (37.8)	34 (34.7)
	IM	42 (42.9)	49 (50.0)
	PM	19 (19.4)	15 (15.3)
	IM + PM	61 (62.2)	64 (65.3)

Data are presented as *n* (%) unless otherwise stated.
Abbreviations: ASO, arteriosclerosis obliterans; EM, extensive metabolizer; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme-A; IM, intermediate metabolizer; MI, myocardial infarction; PM, poor metabolizer; TIA, transient ischemic attack; SD, standard deviation.

Table 2. Incidence of the primary and secondary efficacy endpoints (full analysis set) from the start of administration to 1 day after completion of treatment or discontinuation, and bleeding events (safety analysis set) from the start of administration until 14 days after completion of treatment or discontinuation

	Prasugrel 3.75 mg *N*=118		Clopidogrel 75/50 mg *N*=112		Risk ratio Prasugrel 3.75 mg / Clopidogrel 75/50 mg	
Efficacy endpoints	*n* (%)	[95% CI]	*n* (%)	[95% CI]	Estimate	[95% CI]
Composite primary endpoint[§]	8 (6.8)	[3.0, 12.9]	8 (7.1)	[3.1, 13.6]	0.949	[0.369, 2.443]
Ischemic stroke	7 (5.9)	[2.4, 11.8]	8 (7.1)	[3.1, 13.6]	0.831	[0.311, 2.215]
Myocardial infarction	1 (0.8)	[0.0, 4.6]	0 (0.0)	[0.0, 3.2]	-	[-, -]
Death from other vascular causes	0 (0.0)	[0.0, 3.1]	0 (0.0)	[0.0, 3.2]	-	[-, -]
Ischemic stroke and TIA	7 (5.9)	[2.4, 11.8]	10 (8.9)	[4.4, 15.8]	0.664	[0.262, 1.685]
Stroke	7 (5.9)	[2.4, 11.8]	8 (7.1)	[3.1, 13.6]	0.831	[0.311, 2.215]
Bleeding endpoints	*N*=120		*N*=114		Risk ratio	
Life-threatening bleeding, major bleeding, and clinically relevant bleeding	6 (5.0)	[1.9, 10.6]	4 (3.5)	[1.0, 8.7]	1.425	[0.413, 4.919]
Life-threatening bleeding	0 (0.0)	[0.0, 3.0]	0 (0.0)	[0.0, 3.2]	-	[-, -]
Symptomatic intracranial bleeding	0 (0.0)	[0.0, 3.0]	0 (0.0)	[0.0, 3.2]	-	[-, -]
Major bleeding	1 (0.8)	[0.0, 4.6]	0 (0.0)	[0.0, 3.2]	-	[-, -]
Clinically relevant bleeding	5 (4.2)	[1.4, 9.5]	4 (3.5)	[1.0, 8.7]	1.188	[0.327, 4.312]
Other bleeding	20 (16.7)	[10.5, 24.6]	25 (21.9)	[14.7, 30.6]	0.760	[0.448, 1.290]
Bleeding events leading to discontinuation	2 (1.7)	[0.2, 5.9]	0 (0.0)	[0.0, 3.2]	-	[-, -]
All bleeding events[†]	23 (19.2)	[12.6, 27.4]	28 (24.6)	[17.0, 33.5]	0.780	[0.479, 1.272]

Risk ratio <1 favors prasugrel.
[§]Composite primary endpoint: ischemic stroke, myocardial infarction, and death from other vascular causes.
[†]All bleeding events: life-threatening bleeding, major bleeding, clinically relevant bleeding, and other bleeding.
Abbreviations: CI, confidence interval; TIA, transient ischemic attack.

respectively (hazard ratio [95% CI] 0.79 [0.45–1.41]), and 3.3% (19 of 583 patients) versus 3.9% (23 of 593 patients) for those with small-artery occlusion (hazard ratio [95% CI] 0.82 [0.45–1.50]). PRASTRO-II also reported numerically lower incidences of the composite primary endpoint in patients administered prasugrel versus those administered clopidogrel (3.75 mg prasugrel, 0% [0 of 216 patients]; 2.5 mg prasugrel, 3.3% [7 of 215 patients]; 50 mg clopidogrel, 3.6% [8 of 223 patients])[7].

In this study, the results of other secondary efficacy endpoints were similar between the prasugrel and clopidogrel groups. However, the incidences of ischemic stroke and TIA were numerically lower in the prasugrel group.

In terms of safety, the incidence of bleeding events (life-threatening bleeding, major bleeding, and clinically relevant bleeding) was similar in both groups, which is consistent with the sub-analysis of the PRASTRO-I study[10]. Overall, these results suggest no major safety concerns with prasugrel, compared with clopidogrel, in patients with thrombotic stroke who have risk factors for ischemic stroke recurrence.

Recently, the combination of ticagrelor and aspirin has been shown to reduce the risk of the major combined endpoints of stroke and death compared with aspirin monotherapy; however, increased bleeding has been reported with the combination[12]. As combined use of two agents increases the risk of bleeding, a strong antiplatelet drug that can be safely used as monotherapy is considered necessary.

In CYP2C19 poor metabolizers, the incidence of ischemic stroke, MI, and death from other vascular causes was 1/19 (5.3%) in the prasugrel group and 3/15 (20.0%) in the clopidogrel group, which shows a similar tendency to that reported in the PRASTRO-I study[6]. Therefore, prasugrel appears to be useful in patients with a CYP2C19 poor metabolizer phenotype.

This study was limited in that the efficacy of prasugrel cannot be judged solely from these data owing to the small number of cases. Thus, the efficacy of prasugrel administration in thrombotic stroke patients with risk factors for ischemic stroke recurrence should be evaluated in conjunction with those of the PRASTRO-I and PRASTRO-II studies. There are also several limitations that should be considered when thinking about the application of the

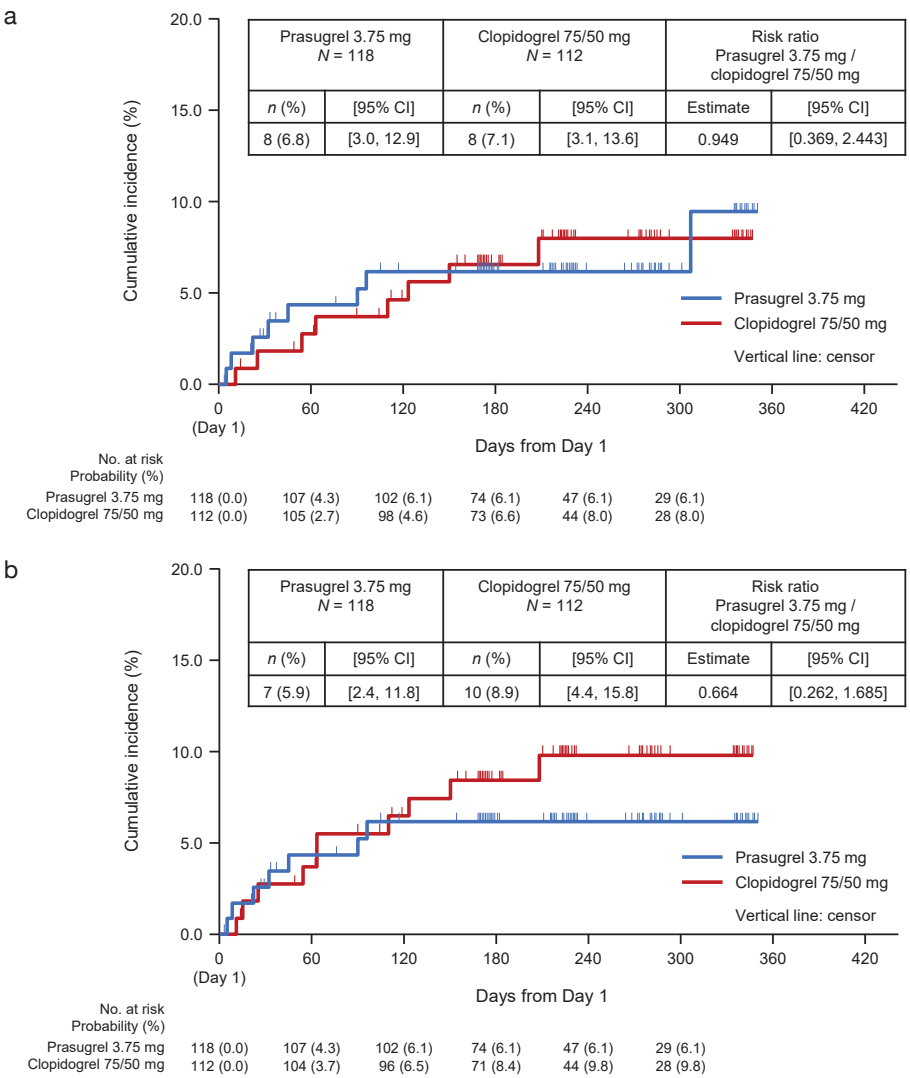

Fig. 2. Kaplan–Meier plot of the cumulative incidence of the primary efficacy endpoint (a composite of ischemic stroke, myocardial infarction, and death from other vascular causes) (a) and ischemic cerebrovascular events (a composite of ischemic stroke and TIA) (b) (full analysis set)

Abbreviations: CI, confidence interval; TIA, transient ischemic attack.

PRASTRO-III data to real-world clinical practice. First, the observation period was limited to 24–48 weeks, which was shorter than that of PRASTRO-I and PRASTRO-II. Second, only patients with a high risk of ischemic stroke were included in this study. Finally, patients were registered ≥ 7 days after the onset of ischemic stroke.

Conclusions

The primary efficacy endpoint in thrombotic stroke patients at high risk of ischemic stroke recurrence was similar in the prasugrel and clopidogrel groups, and no major safety issues were identified in the prasugrel group.

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Conflict of Interest Statement

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Author Contributions

T.K. contributed to the conception or design of the work, interpretation of data, and writing the draft of the manuscript; M.K., Y.M., M.N., K.U., and K.K. contributed to the interpretation of data and writing the draft of the manuscript; H.M., N.K., and J.T. contributed to the conception or design of the work, analysis and interpretation of data, and writing the draft of the manuscript.

Data Sharing Statement

Deidentified individual participant data and relevant supporting clinical trial documents are available on request at https://vivli.org/. In cases where clinical trial data and supporting documents are provided pursuant to Daiichi Sankyo company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants. Details of data-sharing criteria and the procedure for requesting access can be found at https://vivli.org/ourmember/daiichi-sankyo/. Supporting information includes the study protocol, statistical analysis plan, and clinical study report. The access criteria are defined as follows: formal request from qualified scientific and medical researchers on individual participant data and clinical study documents from clinical trials supporting products submitted and licensed in the United States, the European Union, and/or Japan from January 1, 2014 and beyond for the purpose of conducting legitimate research; this must be consistent with the principle of safeguarding study participants' privacy and consistent with provision of informed consent.

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Supplementary Materials

List of Participating Institutions

No.	Institution	Investigator
1	Hirosaki Stroke and Rehabilitation Center	Joji Hagii
2	Hitachi General Hospital	Tsuneo Fujita
3	Jichi Medical University Hospital	Shigeru Fujimoto
4	Institute of Brain and Blood Vessels Mihara Memorial Hospital	Takao Kanzawa
5	Koshigaya Municipal Hospital	Akira Tsunoda
6	Saitama Red Cross Hospital	Shuji Hino
7	Juntendo University Urayasu Hospital	Takao Urabe
8	Jikei University Hospital	Hidetaka Mitsumura
9	Kyorin University Hospital	Teruyuki Hirano
10	Nippon Medical School Hospital	Yasuhiro Nishiyama
11	NTT Medical Center Tokyo	Seiji Okubo
12	Showa General Hospital	Yutaka Honma
13	Tokyo Metropolitan Tama Medical Center	Masayuki Ueda
14	Tokyo Saiseikai Central Hospital	Koichi Oki
15	Tokyo Women's Medical University Hospital	Kazuo Kitagawa
16	Shonan Kamakura General Hospital	Takahisa Mori
17	St. Marianna University School of Medicine Hospital	Yoshihisa Yamano
18	St. Marianna University School of Medicine Toyoko Hospital	Toshihiro Ueda
19	Yokohama Municipal Citizen's Hospital	Osamu Masuo
20	Saiseikai Toyama Hospital	Eisuke Furui
21	Japanese Red Cross Society Azumino Hospital	Yukihiro Kamijo
22	Japanese Red Cross Takayama Hospital	Katsunobu Takenaka
23	Kishiwada Tokushukai Hospital	Hiroyuki Matsumoto
24	Medical Corporation Tokushukai Nozaki Tokushukai Hospital	Hidemitsu Nakagawa
25	National Cerebral and Cardiovascular Center	Masatoshi Koga
26	Osaka General Medical Center	Manabu Sakaguchi
27	Osaka University Hospital	Tsutomu Sasaki
28	Kobe City Medical Center General Hospital	Hirotoshi Imamura
29	Tsukazaki Hospital	Satoru Kosaka
30	Japanese Red Cross Okayama Hospital	Takeshi Iwanaga
31	National Hospital Organization Iwakuni Clinical Center	Kotaro Ogihara
32	Hakujyuji Hospital	Yasuhiro Kumai
33	Japanese Red Cross Fukuoka Hospital	Jiro Kitayama
34	Kyushu Rosai Hospital	Shoji Arihiro
35	National Hospital Organization Fukuoka-Higashi Medical Center	Hiroshi Nakane
36	National Hospital Organization Kyushu Medical Center	Yasushi Okada
37	Our Lady of the Snow Social Medical Corporation St. Mary's Hospital	Kenji Fukuda
38	Steel Memorial Yawata Hospital	Shuji Arakawa
39	Saga-Ken Medical Centre Koseikan	Hiroshi Sugimori
40	Nagasaki University Hospital	Akira Tsujino
41	Japanese Red Cross Kumamoto Hospital	Tadashi Terasaki
42	Saiseikai Kumamoto Hospital	Toshiro Yonehara
43	National Hospital Organization Kagoshima Medical Center	Hideki Matsuoka

Supplemental Methods

Additional Inclusion Criteria

Patients were included if they had one or more of the following risk factors: hypertension, defined as a systolic blood pressure of 140 mmHg and diastolic blood pressure of ≥ 90 mmHg; diabetes, defined as a glycated hemoglobin ≥ 6.5%; chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 or urinary protein ≥ 1+; dyslipidemia, defined as low-density lipoprotein cholesterol ≥ 120 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, and/or triglycerides ≥ 150 mg/dL; and history of ischemic stroke prior to onset of the last attack. Patients who were able to start study drug administration in the period between 7 days to 26 weeks after the last ischemic stroke were also included. If any of the previously mentioned risk factors (hypertension, diabetes, chronic kidney disease, or dyslipidemia) were not met owing to drug therapy, those with two or more risk factors were included.

Exclusion Criteria

The exclusion criteria were as follows: patients with cardioembolic ischemic stroke, paradoxical cerebral embolism, or asymptomatic ischemic stroke; patients with atrial fibrillation or other cardiovascular diseases that cause cardiogenic cerebral embolism; patients with symptomatic non-traumatic intracerebral hemorrhage or a history of such (excluding asymptomatic micro-bleeding that could be seen only in magnetic resonance imaging findings); patients with or at high risk of subarachnoid hemorrhage; patients with or at high risk of bleeding; and patients who received clopidogrel for 22 days or more after the last ischemic stroke and before the start of study drug administration.

Definitions of Efficacy Events

Ischemic stroke was defined as the presence of new neurologic symptoms or signs of ischemic stroke in which the culprit lesion was detected by computed tomography (CT) or magnetic resonance imaging (MRI).

Myocardial infarction refers to cases diagnosed based on ischemic conditions of the chest, myocardial enzyme release, electrocardiogram, and other relevant findings.

Death from other vascular causes was defined as deaths resulting from damage to the vessels other than cerebral or cardiac vessels (e.g., pulmonary embolism). However, this group did not include cases in which bleeding, not ischemia, was the obvious cause of death.

Transient ischemic attack was defined as transient episodes of neurologic dysfunction caused by focal cerebral, spinal cord, and retinal ischemia, in which CT and MRI scans revealed no evidence of acute infarction.

Stroke was defined as the presence of new neurologic symptoms or signs with the presence of a new infarct lesion detected by CT or MRI and considered related to the neurologic symptoms or signs.

Definitions of Bleeding Events

The following bleeding episodes were classified as life-threatening bleeding: fatal bleeding, bleeding causing a decrease in hemoglobin level of 5 g/dL or more, bleeding that reduces blood pressure to a level that needs to be elevated by use of a cardiac agent, symptomatic intracranial hemorrhage, and bleeding requiring blood transfusion of eight or more units of red blood cells (or equivalent amount of whole blood).

Major bleeding was defined as bleeding episodes that are not considered life-threatening bleeding events, but meet one or more of the following criteria: bleeding leading to significant dysfunction, intraocular hemorrhage leading to significant loss of sight, bleeding requiring blood transfusion of less than eight units of red blood cells (or equivalent amount of whole blood).

Clinically relevant bleeding was defined as bleeding episodes that are not considered life-threatening bleeding or major bleeding events, but meet one or more of the following criteria: bleeding at significant sites (e.g., retroperitoneum, pericardial space, posterior chamber of the eye [vitreous hemorrhage, retinal hemorrhage], spinal cavity, intraarticular space), gastrointestinal hemorrhage accompanied by decreased hemoglobin level (unrelated to intubation or nasogastric tube placement), macroscopic hematuria involving no apparent external cause, epistaxis needing otolaryngologic treatment, gingival bleeding requiring dental or periodontal treatment, and bleeding judged by the investigators as requiring discontinuation or temporary discontinuation of the study drug.

Other bleeding was defined as all bleeding episodes that are not classified as life-threatening, major, or clinically relevant bleeding.

Genetic Polymorphism Analysis

Blood samples (2 mL) were collected from subjects who provided informed consent for genetic polymorphism analysis of CYP2C19 once before Week 8 (Visit 5) of the treatment period after randomization. Genetic analysis was performed by an independent laboratory (SRL Mediserch Inc., Tokyo,

Japan). The frequency of genetic polymorphisms of CYP2C19 was calculated by treatment group. Patients were classified as extensive metabolizers, intermediate metabolizers, or poor metabolizers.

Sample Size Calculations

The target number of cases was set at 250 (125 subjects per group). A minimum number of subjects was set to increase the probability that the point estimate of the risk ratio of the prasugrel group to the clopidogrel group would be <1 for the incidence of the primary efficacy endpoint. Based on the results of previous studies in populations similar to the target population in this study (unpublished data), the incidence of the primary efficacy endpoint which would be observed in the clopidogrel group within 48 weeks after the start of administration of the study drug was estimated to be 4%. It was also estimated that the risk ratio of the primary efficacy endpoint (prasugrel group/clopidogrel sulfate group) would be between 0.4 and 0.8. The probability that the point estimate of the risk ratio would be <1 when simulations were performed 10,000 times with 110 patients per group in this study was as follows: for a true risk ratio of 0.4, 0.5, 0.6, 0.7, and 0.8, the probability that the point estimate of the risk ratio would be <1 is 81.2%, 75.1%, 68.7%, 62.3%, and 55.9%, respectively.

Definitions of the Analysis Sets

The full analysis set comprised randomly assigned subjects who did not meet any of the following criteria: major Good Clinical Practice violation, subjects who did not meet the inclusion criteria, subjects who did not take the study drug at all, and subjects who did not have available data for the primary endpoint after study drug administration.

The safety analysis set comprised all randomly assigned subjects who received at least one tablet of the study drug.

The pharmacodynamic analysis set comprised all subjects who had available data for the pharmacodynamic endpoint at one or more time points after study drug administration.

The gene analysis set comprised all subjects who provided informed consent for collection of blood specimens for genetic polymorphism analysis of CYP2C19 and underwent measurements.

Supplementary Table 1. Incidence of the primary efficacy endpoint (a composite of ischemic stroke, myocardial infarction, and death from other vascular causes) from the start of administration to the end of the follow-up period or discontinuation (full analysis set)

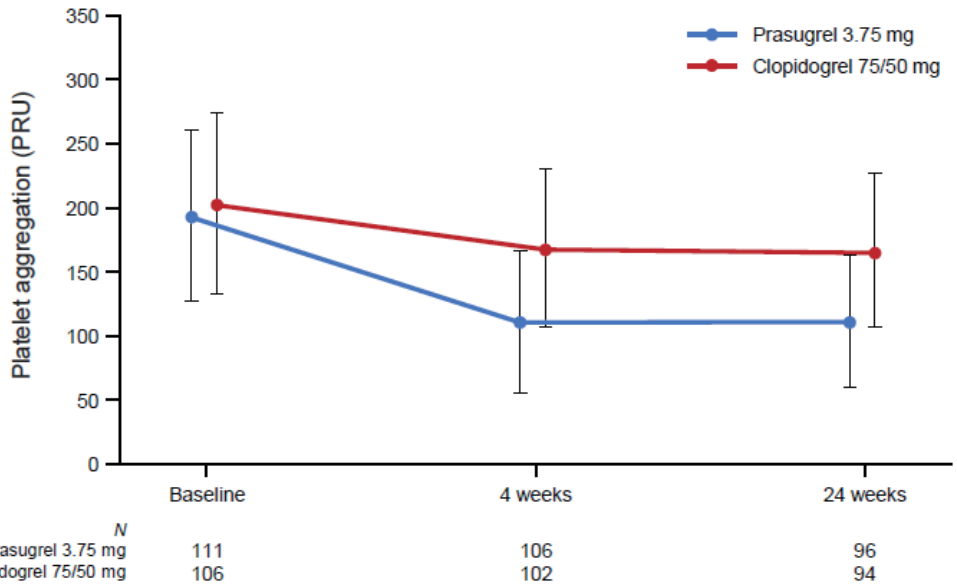
	Prasugrel 3.75 mg *N*=118		Clopidogrel 75/50 mg *N*=112		Risk ratio Prasugrel 3.75 mg / Clopidogrel 75/50 mg		Hazard ratio Prasugrel 3.75 mg / Clopidogrel 75/50 mg	
Endpoints	*n* (%)	[95% CI]	*n* (%)	[95% CI]	Estimate	[95% CI]	Estimate	[95% CI]
Cerebro-cardiovascular events[a]	8 (6.8)	[3.0, 12.9]	8 (7.1)	[3.1, 13.6]	0.949	[0.369, 2.443]	0.961	[0.361, 2.560]
Ischemic stroke	7 (5.9)	[2.4, 11.8]	8 (7.1)	[3.1, 13.6]	0.831	[0.311, 2.215]	0.840	[0.305, 2.317]
Myocardial infarction	1 (0.8)	[0.0, 4.6]	0 (0.0)	[0.0, 3.2]	-	[-, -]	-	[-, -]
Death from other vascular causes	0 (0.0)	[0.0, 3.1]	0 (0.0)	[0.0, 3.2]	-	[-, -]	-	[-, -]
Ischemic stroke and TIA	7 (5.9)	[2.4, 11.8]	10 (8.9)	[4.4, 15.8]	0.664	[0.262, 1.685]	0.665	[0.253, 1.747]
Stroke	7 (5.9)	[2.4, 11.8]	8 (7.1)	[3.1, 13.6]	0.831	[0.311, 2.215]	0.840	[0.305, 2.317]

Risk ratio and hazard ratio <1 favors prasugrel.
[a]Cerebro-cardiovascular events: ischemic stroke, myocardial infarction, and death from other vascular causes.
CI, confidence interval; TIA, transient ischemic attack.

Supplementary Table 2. Patients experiencing AEs (safety analysis set)

	Prasugrel 3.75 mg *N*=120	Clopidogrel 75/50 mg *N*=114
All AEs	92 (76.7)	94 (82.5)
Drug-related AEs	14 (11.7)	17 (14.9)
All SAEs	22 (18.3)	19 (16.7)
Death	1 (0.8)	1 (0.9)
SAEs that did not lead to death	21 (17.5)	18 (15.8)
Drug-related SAEs	0 (0.0)	4 (3.5)
Death	0 (0.0)	0 (0.0)
SAEs that did not lead to death	0 (0.0)	4 (3.5)
All severe AEs	4 (3.3)	5 (4.4)
Drug-related severe AEs	0 (0.0)	0 (0.0)
All AEs leading to withdrawal from the study	16 (13.3)	17 (14.9)
Drug-related AEs leading to withdrawal from the study	2 (1.7)	2 (1.8)

Data are shown as *n* (%).
AEs, adverse events; SAEs, serious adverse events.



Supplementary Fig. 1. Change in PRU levels (pharmacodynamic analysis set)

The PRU level decreased from 193.4 at baseline to 111.2 at 4 weeks and 111.6 at 24 weeks in the prasugrel group. In the clopidogrel group, the PRU value decreased from 203.1 at baseline to 168.6 at 4 weeks and 166.6 at 24 weeks. The between-group difference (prasugrel – clopidogrel group) was –57.4 (95% CI –73.4, –41.3) at 4 weeks and –55.0 (95% CI –71.0, –39.0) at 24 weeks.
CI, confidence interval; PRU, $P2Y_{12}$ reaction unit.

Supplementary Table 3. Incidence of the primary and secondary efficacy endpoints from the start of administration to 1 day after completion of treatment or discontinuation according to CYP genetic polymorphism

	Prasugrel 3.75 mg *N*=118			Clopidogrel 75/50 mg *N*=112			Risk ratio Prasugrel 3.75 mg / Clopidogrel 75/50 mg	
Endpoints	*N*	*n* (%)	[95% CI]	*N*	*n* (%)	[95% CI]	Estimate	[95% CI]
Composite primary endpoint[a]								
EM	37	4 (10.8)	[3.0, 25.4]	34	2 (5.9)	[0.7, 19.7]	1.838	[0.359, 9.401]
IM	42	2 (4.8)	[0.6, 16.2]	49	2 (4.1)	[0.5, 14.0]	1.167	[0.172, 7.927]
PM	19	1 (5.3)	[0.1, 26.0]	15	3 (20.0)	[4.3, 48.1]	0.263	[0.030, 2.281]
Missing	20	1 (5.0)	[0.1, 24.9]	14	1 (7.1)	[0.2, 33.9]	0.700	[0.048, 10.275]
Ischemic stroke								
EM	37	3 (8.1)	[1.7, 21.9]	34	2 (5.9)	[0.7, 19.7]	1.378	[0.245, 7.756]
IM	42	2 (4.8)	[0.6, 16.2]	49	2 (4.1)	[0.5, 14.0]	1.167	[0.172, 7.927]
PM	19	1 (5.3)	[0.1, 26.0]	15	3 (20.0)	[4.3, 48.1]	0.263	[0.030, 2.281]
Missing	20	1 (5.0)	[0.1, 24.9]	14	1 (7.1)	[0.2, 33.9]	0.700	[0.048, 10.275]
Myocardial infarction								
EM	37	1 (2.7)	[0.1, 14.2]	34	0 (0.0)	[0.0, 10.3]	-	[-, -]
IM	42	0 (0.0)	[0.0, 8.4]	49	0 (0.0)	[0.0, 7.3]	-	[-, -]
PM	19	0 (0.0)	[0.0, 17.6]	15	0 (0.0)	[0.0, 21.8]	-	[-, -]
Missing	20	0 (0.0)	[0.0, 16.8]	14	0 (0.0)	[0.0, 23.2]	-	[-, -]
Death from other vascular causes								
EM	37	0 (0.0)	[0.0, 9.5]	34	0 (0.0)	[0.0, 10.3]	-	[-, -]
IM	42	0 (0.0)	[0.0, 8.4]	49	0 (0.0)	[0.0, 7.3]	-	[-, -]
PM	19	0 (0.0)	[0.0, 17.6]	15	0 (0.0)	[0.0, 21.8]	-	[-, -]
Missing	20	0 (0.0)	[0.0, 16.8]	14	0 (0.0)	[0.0, 23.2]	-	[-, -]
Ischemic stroke and TIA								
EM	37	3 (8.1)	[1.7, 21.9]	34	3 (8.8)	[1.9, 23.7]	0.919	[0.199, 4.248]
IM	42	2 (4.8)	[0.6, 16.2]	49	3 (6.1)	[1.3, 16.9]	0.778	[0.136, 4.436]
PM	19	1 (5.3)	[0.1, 26.0]	15	3 (20.0)	[4.3, 48.1]	0.263	[0.030, 2.281]
Missing	20	1 (5.0)	[0.1, 24.9]	14	1 (7.1)	[0.2, 33.9]	0.700	[0.048, 10.275]
Stroke								
EM	37	3 (8.1)	[1.7, 21.9]	34	2 (5.9)	[0.7, 19.7]	1.378	[0.245, 7.756]
IM	42	2 (4.8)	[0.6, 16.2]	49	2 (4.1)	[0.5, 14.0]	1.167	[0.172, 7.927]
PM	19	1 (5.3)	[0.1, 26.0]	15	3 (20.0)	[4.3, 48.1]	0.263	[0.030, 2.281]
Missing	20	1 (5.0)	[0.1, 24.9]	14	1 (7.1)	[0.2, 33.9]	0.700	[0.048, 10.275]

N=Number of subjects with available data for each endpoint. Risk ratio <1 favors prasugrel.
[a]Composite primary endpoint: ischemic stroke, myocardial infarction, and death from other vascular causes.
CI, confidence interval; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; TIA, transient ischemic attack.