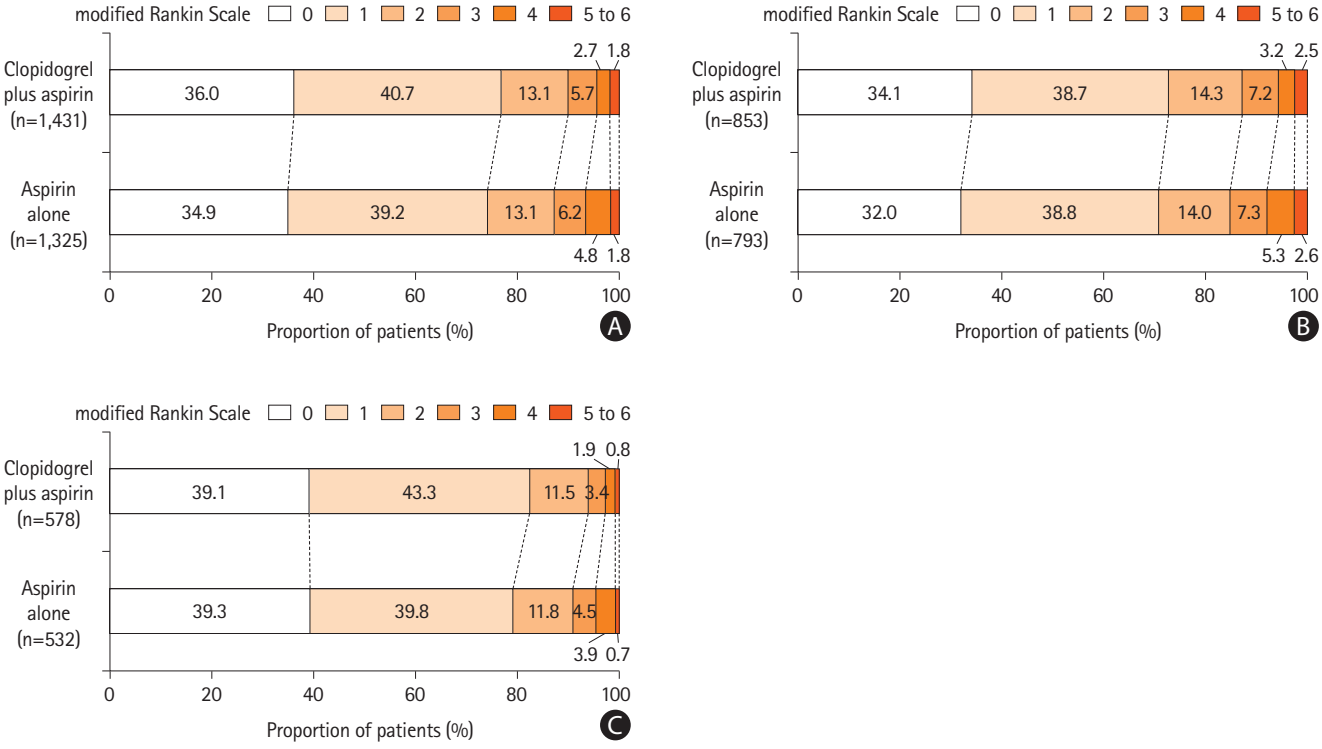
Supplementary Results

Sensitivity analysis in the per-protocol analysis set



Supplementary Figure 1. Distribution of modified Rankin Scale score at 90 days. The raw distribution of scores is shown (A) across time from symptom onset to antiplatelet therapy, (B) in 0–24 h time subgroup, and (C) in 24–48 time subgroup. The scores ranged from 0 to 6 (0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability; and 6=death).

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Subgroup	Clopidogrel plus aspirin	Aspirin alone	RD,% (95% CI)	P Value for trend	P Value for interaction
Age					
Age < 65 years					0.17
0-24h group	17/385 (4.4%)	27/338 (8.0%)	-3.6 (-7.2 to 0.0)	0.048	
24-48h group	9/258 (3.5%)	7/244 (2.9%)	0.6 (-2.5 to 3.7)	0.69	
Age ≥ 65 years					0.38
0-24h group	25/470 (5.3%)	38/458 (8.3%)	-3.0 (-6.2 to 0.3)	0.07	
24-48h group	8/320 (2.5%)	7/290 (2.4%)	0.1 (-2.4 to 2.5)	0.95	
Sex					
Female					0.19
0-24h group	17/285 (6.0%)	22/273 (8.1%)	-2.1 (-6.3 to 2.1)	0.33	
24-48h group	7/217 (3.2%)	3/192 (1.6%)	1.7 (-1.3 to 4.6)	0.27	
Male					0.32
0-24h group	25/570 (4.4%)	43/523 (8.2%)	-3.8 (-6.7 to -0.9)	0.009	
24-48h group	10/361 (2.8%)	11/342 (3.2%)	-0.4 (-3.0 to 2.1)	0.73	
History of diabetes					
Yes					0.55
0-24h group	11/237 (4.6%)	18/193 (9.3%)	-4.7 (-9.6 to 0.2)	0.06	
24-48h group	5/145 (3.4%)	6/129 (4.7%)	-1.2 (-5.9 to 3.5)	0.62	
No					0.12
0-24h group	31/618 (5.0%)	47/603 (7.8%)	-2.8 (-5.5 to 0.0)	0.047	
24-48h group	12/433 (2.8%)	8/405 (2.0%)	0.8 (-1.3 to 2.9)	0.45	
History of hypertension					
Yes					0.27
0-24h group	24/509 (4.7%)	41/493 (8.3%)	-3.6 (-6.7 to -0.5)	0.02	
24-48h group	10/376 (2.7%)	9/333 (2.7%)	0.0 (-2.4 to 2.3)	0.97	
No					0.24
0-24h group	18/346 (5.2%)	24/303 (7.9%)	-2.7 (-6.6 to 1.1)	0.16	
24-48h group	7/202 (3.8%)	5/201 (2.5%)	1.0 (-2.3 to 4.3)	0.56	
NIHSS score at admission					
4 to 7					0.1
0-24h group	36/739 (4.9%)	56/699 (8.0%)	-3.1 (-5.7 to -0.6)	0.02	
24-48h group	17/535 (3.2%)	13/489 (2.7%)	0.5 (-1.5 to 2.6)	0.62	
8 to 10					0.99
0-24h group	6/116 (5.2%)	9/97 (9.3%)	-4.1 (-11.1 to 2.9)	0.25	
24-48h group	0/43 (0.0%)	1/45 (2.2%)	-2.2 (NA to NA)	0.33	
Presumed stroke cause					
Large artery atherosclerosis					0.99
0-24h group	5/73 (6.8%)	7/48 (14.6%)	-7.7 (-19.3 to 3.8)	0.19	
24-48h group	0/39 (0.0%)	5/47 (10.6%)	-10.6 (NA to NA)	0.1	
Small artery occlusion					0.36
0-24h group	24/280 (8.6%)	22/272 (8.1%)	0.5 (-4.1 to 5.1)	0.84	
24-48h group	8/158 (5.1%)	4/155 (2.6%)	2.5 (-1.8 to 6.7)	0.25	
Undetermined cause					0.01
0-24h group	12/495 (2.4%)	36/472 (7.6%)	-5.2 (-8.0 to -2.5)	0.001	
24-48h group	9/378 (2.4%)	5/330 (1.5%)	0.9 (-1.2 to 2.9)	0.4	
Total					**0.12**
0-24h group	42/855 (4.9%)	65/796 (8.2%)	-3.3 (-5.6 to -0.9)	0.008	
24-48h group	17/578 (2.9%)	14/534 (2.6%)	0.3 (-1.6 to 2.3)	0.54	

Supplementary Figure 2. Subgroup analysis of the effect of antiplatelet therapy on the primary outcome in time subgroups. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. The analysis was not powered and had no pre-specified correction for multiple comparisons for definitive analysis of the subgroups. NIHSS, National Institutes of Health Stroke Scale; RD, risk difference; CI, confidence interval.

Supplementary Table 1. Baseline characteristics of patients in the analysis

	0–24 h group				24–48 h group				
	Total patients (n=1,651)	Clopidogrel +aspirin (n=855)	Aspirin alone (n=796)	*P*	Total patients (n=1,112)	Clopidogrel +aspirin (n=578)	Aspirin alone (n=534)	*P*	*P*
Age (yr)	66 (59–74)	66 (58–73)	67 (59–74)	0.22	66 (58–73)	66 (58–72)	65 (58–74)	0.86	0.06
Sex				0.68				0.58	0.11
Male	1,093 (66.2)	570 (66.7)	523 (65.7)		703 (63.2)	361 (62.5)	342 (64.0)		
Female	558 (33.8)	285 (33.3)	273 (34.3)		409 (36.8)	217 (37.5)	192 (36.0)		
Current smoking	582/1,639 (35.5)	315/848 (37.1)	267/791 (33.8)	0.15	319/1,102 (28.9)	161/573 (28.1)	158/529 (29.9)	0.52	<0.01
Current drinking*	348/1,637 (21.3)	188/846 (22.2)	160/791 (20.2)	0.32	192/1,102 (17.4)	92/574 (16.0)	100/528 (18.9)	0.20	0.01
Comorbidities†									
Hypertension	1,002 (60.7)	509 (59.5)	493 (61.9)	0.32	709 (63.8)	376 (65.1)	333 (62.4)	0.35	0.10
Diabetes	430 (26.0)	237 (27.7)	193 (24.2)	0.11	274 (24.6)	145 (25.1)	129 (24.2)	0.72	0.41
Previous stroke‡	514/1,641 (31.3)	257/847 (30.3)	257/794 (32.4)	0.38	377/1,107 (34.1)	198/575 (34.4)	179/532 (33.6)	0.78	0.13
Previous transient ischemic attack	7/1,642 (0.4)	5/852 (0.6)	2/790 (0.3)	0.30	1/1,108 (0.1)	0/577 (0.0)	1/531 (0.2)	0.30	0.11
Blood pressure at randomization									
Systolic (mm Hg)	153 (140–170)	153 (140–170)	153 (140–170)	0.95	150 (140–167)	150 (140–169)	151 (140–165)	0.73	0.33
Diastolic (mm Hg)	90 (80–98)	90 (80–98)	90 (80–98)	0.27	90 (80–100)	90 (80–100)	90 (80–98)	0.14	0.56
Blood glucose (mmol/L)	6.1 (5.2–7.9)	6.1 (5.3–8.0)	6.0 (5.2–7.8)	0.23	6.1 (5.2–8.1)	6.0 (5.3–8.0)	6.1 (5.1–8.2)	0.63	0.98
NIHSS score at randomization§	5 (4–6)	5 (4–6)	5 (4–6)	0.43	4 (4–6)	4 (4–6)	4 (4–6)	0.40	<0.01
Estimated premorbid function (mRS)‖				0.52				0.81	0.59
No symptoms	1,172 (71.0)	601 (70.3)	571 (71.7)		800 (71.9)	414 (71.6)	386 (72.3)		
Symptoms without disability	479 (29.0)	254 (29.7)	225 (28.3)		312 (28.1)	164 (28.44)	148 (27.7)		
Time from symptom onset to antiplatelet therapy	9.0 (5.5–14.5)	8.8 (5.2–14.1)	9.0 (6.0–14.9)	0.47	28.5 (25.1–41.3)	28.0 (25.1–40.0)	29.0 (25.1–42.3)	0.21	<0.01
Presumed stroke cause¶				0.22				0.48	0.03
Undetermined cause	967/1,646 (58.7)	495/852 (58.1)	472/794 (59.4)		708 (65.4)	378 (65.4)	330 (61.8)		
Small artery occlusion	552/1,646 (33.5)	280/852 (32.9)	272/794 (34.3)		313 (28.1)	158 (27.3)	155 (29.0)		
Large artery atherosclerosis	121/1,646 (7.4)	73/852 (8.6)	48/794 (6.0)		86 (7.7)	39 (6.7)	47 (8.8)		
Other determined cause	6/1,646 (0.4)	4/852 (0.5)	2/794 (0.3)		5 (0.4)	3 (0.5)	2 (0.4)		
Location of responsible vessel				0.25				0.13	<0.01
Anterior circulation infarction	1,030/1,415 (72.8)	539/754 (71.5)	491/661 (74.3)		642/964 (66.6)	324/506 (64.00)	318/458 (69.4)		
Posterior circulation infarction	339/1,415 (24.0)	193/754 (25.6)	146/661 (22.1)		293/964 (30.4)	168/506 (33.2)	125/458 (27.3)		
Anterior and posterior circulation infarction	22/1,415 (2.9)	22/754 (2.9)	24/661 (3.6)		29/964 (3.0)	14/506 (2.8)	15/458 (3.3)		

The data are shown with median (IQR) for continuous characteristics or frequency (percentages) for categorical characteristics.
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; NA, not applicable.
*Current drinker means consuming alcohol at least once a week within 1 year before onset of the disease and consuming alcohol continuously for more than 1 year; †The comorbidities were based on the patient or family report; ‡Previous ischemic stroke referred only to the patients with prestroke mRS ≤1; §Patients with NIHSS scores of 6 to 16 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit; ‖Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death). No symptoms indicates scoring 0 and symptoms without disability indicates scoring 1; ¶The presumed stroke cause was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system[1] using clinical findings, brain imaging, and laboratory tests. Other determined causes included pulmonary embolism, peripheral vessel incident, and cardiovascular incident.

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Supplementary Table 2. Association between the continuous time from symptom onset with the start antiplatelet therapy with outcomes

	Clopidogrel +aspirin (n=1,433)	Aspirin alone (n=1,330)	Treatment effect metric	Model 1*		Model 2†		Model 3‡		P_{int}
				Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	
Primary outcome										
END§ at 7 days	59/1,433 (4.1)	79/1,330 (5.9)	RD‖	-1.8 (-3.5 to -0.2)	0.03	-1.8 (-3.0 to -0.7)	<0.01	-1.8 (-3.0 to -0.7)	<0.01	0.48
Secondary outcomes										
mRS¶ 0–1 at 90 days	1,097/1,431 (76.7)	983/1,325 (74.2)	RD‖	2.5 (-0.7 to 5.7)	0.13	2.5 (0.2 to 4.7)	0.03	2.5 (0.2 to 4.7)	0.03	0.83
mRS¶ at 90 days	NA	NA	OR**	1.10 (0.96 to 1.26)	0.19	1.10 (0.99 to 1.21)	0.06	1.10 (0.99 to 1.21)	0.06	0.76
Change in NIHSS†† at 14 days	-0.56 (-1.01 to -0.25)	-0.56 (-1.10 to -0.22)	GMR‖	-0.01 (-0.05 to 0.04)	0.75	-0.01 (-0.04 to 0.03)	0.65	-0.01 (-0.04 to 0.03)	0.65	0.99
New stroke‡‡ within 90 days	12/1,431 (0.8)	13/1,325 (1.0)	HR§§	0.86 (0.39 to 1.87)	0.70	0.86 (0.39 to 1.89)	0.71	0.88 (0.40 to 1.94)	0.75	0.29
Other vascular events‖‖ or death within 90 days	16/1,431 (1.1)	11/1,325 (0.8)	HR§§	1.35 (0.63 to 2.91)	0.45	1.31 (0.61 to 2.82)	0.49	1.41 (0.65 to 3.05)	0.39	0.21
Safety outcomes¶¶										
Any bleeding events	7/1,433 (0.5)	10/1,330 (0.8)	RD‖	-0.3 (-0.9 to 0.3)	0.38	-0.3 (-0.7 to 0.1)	0.21	-0.3 (-0.7 to 0.1)	0.21	0.05
Intracranial hemorrhage	1/1,433 (0.1)	2/1,330 (0.2)	RD‖	-0.1 (-0.3 to 0.2)	0.53	-0.1 (-0.3 to 0.31)	0.36	-0.1 (-0.3 to 0.1)	0.36	0.85

The data are shown with median (IQR) for continuous characteristics or frequency (percentages) for categorical characteristics unless otherwise indicated.
CI, confidence interval; END, early neurological deterioration; GMR, geometric mean ratio; HR, hazard ratio; IQR, interquartile range; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RD, risk difference; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Unadjusted analysis in the model; †Adjusted for time from symptom onset to antiplatelet therapy in the model; ‡Adjusted for time from symptom onset to antiplatelet therapy and prespecified covariates (age, sex, history of diabetes, history of hypertension, NIHSS score at randomization, and presumed stroke cause based on the TOAST classification[1]); §END was defined as an increase between baseline and 7 days of ≥2 on the NIHSS score, but not as result of cerebral hemorrhage[2]; ‖Calculated using the generalized liner model; ¶Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death); **A shift measures of function according to the full range of scores on the mRS at 90 days was analyzed by ordinal logistic regression, and the chi-square for the likelihood ratio test were 7.34 (*P*=0.20) in the model 1, 13.19 (*P*=0.10) in the model 2, and 15.20 (*P*=0.11) in the model 3; ††Patients with NIHSS scores of 4 to 10 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit. The log(NIHSS+1) was analyzed using generalized linear model; ‡‡New stroke included ischemic stroke and hemorrhagic stroke; §§Calculated using the Cox regression model; ‖‖Other vascular events included pulmonary embolism, peripheral vascular, or cardiovascular event; ¶¶The safety outcomes were analyzed based on the safety analysis set of the ATAMIS trial.

Supplementary Table 3. Association between categorical time from symptom onset with the start antiplatelet therapy with outcomes

	Time	Clopidogrel+aspirin (n=1,433)	Aspirin alone (n=1,330)	Treatment effect metric	Model 1*		Model 4†		Model 5‡		P_{int}
					Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	
Primary outcome											
END§ at 7 days	0–24 h	42/855 (4.9)	65/796 (8.2)	RD‖	-3.3 (-5.6 to -0.9)	<0.01	-3.3 (-5.6 to -0.9)	<0.01	-3.4 (-5.1 to -1.7)	<0.01	<0.05
	24–48 h	17/578 (2.9)	14/534 (2.6)		0.3 (-1.6 to 2.3)	0.75	0.3 (-1.6 to 2.3)	0.75	0.3 (-1.0 to 1.7)	0.65	
Secondary outcomes											
mRS¶ 0–1 at 90 days	0–24 h	624/853 (72.8)	562/793 (70.9)	RD‖	1.9 (-2.4 to 6.3)	0.38	1.9 (-2.4 to 6.3)	0.38	2.2 (-0.9 to 5.3)	0.16	0.92
	24–48 h	476/578 (82.4)	421/532 (79.1)		3.2 (-1.4 to 7.9)	0.18	3.2 (-1.4 to 7.9)	0.18	3.2 (-0.1 to 6.5)	0.05	
mRS¶ at 90 days	0–24 h	NA	NA	OR**	1.11 (0.93 to 1.33)	0.23	1.11 (0.93 to 1.33)	0.23	1.12 (0.99 to 1.27)	0.07	0.29
	24–48 h	NA	NA		1.07 (0.86 to 1.33)	0.57	1.07 (0.86 to 1.33)	0.57	1.07 (0.91 to 1.25)	0.41	
Change in NIHSS†† at 14 days	0–24 h	-0.51 (-0.91 to -0.22)	-0.51 (-0.98 to -0.22)	GMR‖	0.01 (-0.06 to 0.07)	0.88	0.01 (-0.06 to 0.07)	0.88	0.01 (-0.04 to 0.05)	0.74	0.40
	24–48 h	-0.56 (-1.10 to -0.25)	-0.69 (-1.10 to -0.34)		-0.03 (-0.10 to 0.04)	0.46	-0.03 (-0.10 to 0.04)	0.46	-0.03 (-0.08 to 0.02)	0.29	
New stroke‡‡ within 90 days	0–24 h	5/853 (0.6)	9/793 (1.1)	HR§§	0.52 (0.17 to 1.54)	0.24	0.52 (0.17 to 1.56)	0.24	0.54 (0.18 to 1.61)	0.27	0.12
	24–48 h	7/578 (1.2)	4/532 (0.8)		1.61 (0.47 to 5.50)	0.45	1.61 (0.47 to 5.49)	0.45	1.73 (0.50 to 5.94)	0.39	
Other vascular events‖‖ or death within 90 days	0–24 h	13/853 (1.5)	10/819 (1.3)	HR§§	1.10 (0.49 to 2.46)	0.81	1.12 (0.50 to 2.51)	0.78	1.32 (0.58 to 3.04)	0.51	0.50
	24–48 h	3/578 (0.5)	1/532 (0.2)		2.76 (0.29 to 26.49)	0.38	2.75 (0.29 to 26.44)	0.38	2.18 (0.20 to 24.26)	0.53	
Safety outcomes¶¶											
Any bleeding events	0–24 h	3/855 (0.4)	8/796 (1.0)	RD‖	-0.7 (-1.5 to 0.1)	0.11	-0.7 (-1.5 to 0.1)	0.11	-0.7 (-1.3 to -0.1)	0.02	0.10
	24–48 h	4/578 (0.7)	2/534 (0.4)		0.3 (-0.5 to 1.2)	0.47	0.3 (-0.5 to 1.2)	0.47	0.3 (-0.3 to 0.9)	0.30	
Intracranial hemorrhage	0–24 h	1/855 (0.1)	2/796 (0.3)	RD‖	-0.1 (-0.6 to 0.3)	0.53	-0.1 (-0.6 to 0.3)	0.53	-0.1 (-0.4 to 0.2)	0.37	0.99
	24–48 h	0/578 (0.0)	0/534 (0.0)		NA	NA	NA	NA	NA	NA	

The data are shown with median (IQR) for continuous characteristics or frequency (percentages) for categorical characteristics.
CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RD, risk difference; OR, odds ratio; GMR, geometric mean ratio; HR, hazard ratio; IQR, interquartile range; NA, not applicable.
*Unadjusted analysis in the model; †Adjusted for unbalanced covariates between clopidogrel plus aspirin group and aspirin alone group. Given that there was no imbalanced characteristic between two treatment groups in any time subgroup, the results in the model were as same as those in model 1; ‡Adjusted for prespecified covariates (age, sex, history of diabetes, history of hypertension, NIHSS score at randomization, and presumed stroke cause based on the TOAST classification[1]) and unbalanced covariates between clopidogrel plus aspirin group and aspirin alone group; §END was defined as an increase between baseline and 7 days of ≥2 on the NIHSS score, but not as result of cerebral hemorrhage[2]; ‖Calculated using the generalized liner model; ¶Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death); **A shift measures of function according to the full range of scores on the mRS at 90 days was analyzed by ordinal logistic regression, and the chi-square for the likelihood ratio test were 4.0 (*P*=0.55) and 6.4 (*P*=0.27) in the model 1, 4.0 (*P*=0.55) and 6.4 (*P*=0.27) in the model 4, and 50.6 (*P*=0.26) and 67.2 (*P*=0.19) in the model 5; ††Patients with NIHSS scores of 4 to 10 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit. The log(NIHSS+1) was analyzed using generalized linear model; ‡‡New stroke included ischemic stroke and hemorrhagic stroke; §§Calculated using the Cox regression model; ‖‖Other vascular events included pulmonary embolism, peripheral vascular, or cardiovascular event; ¶¶The safety outcomes were analyzed based on the safety analysis set of the ATAMIS trial.

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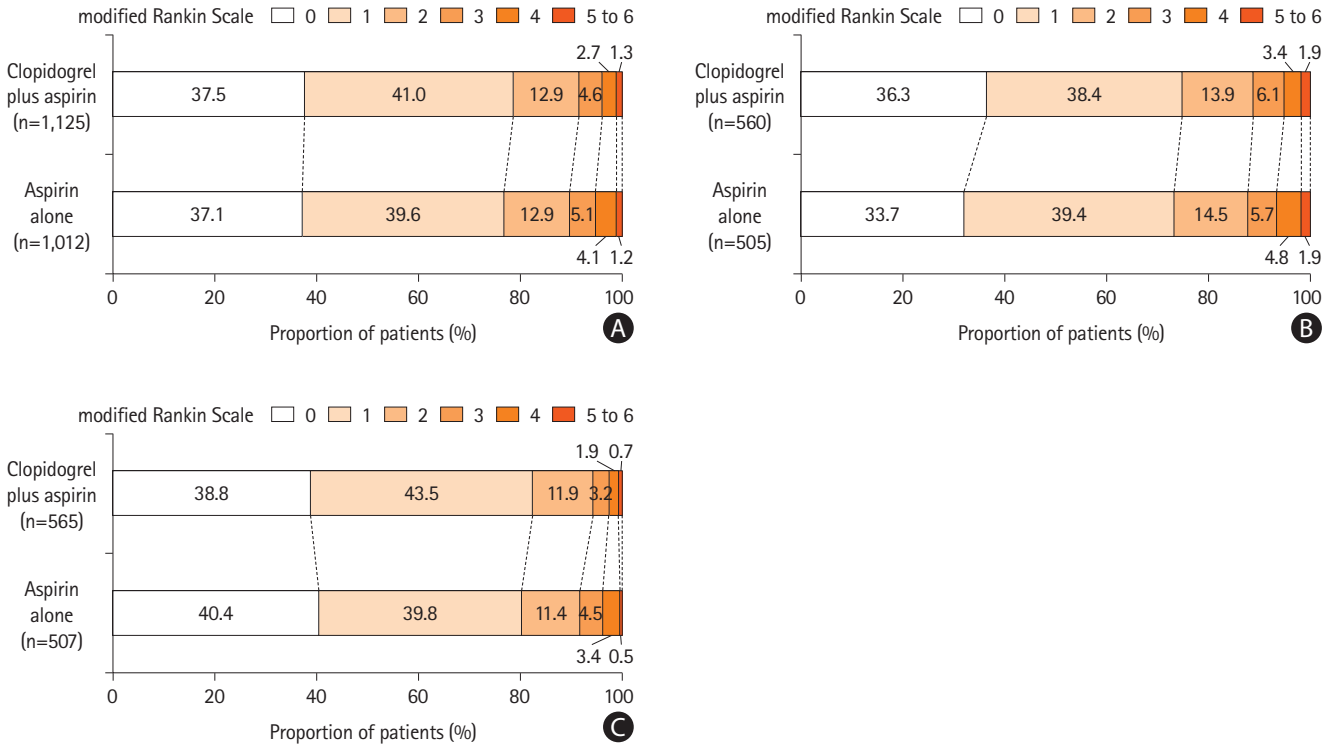
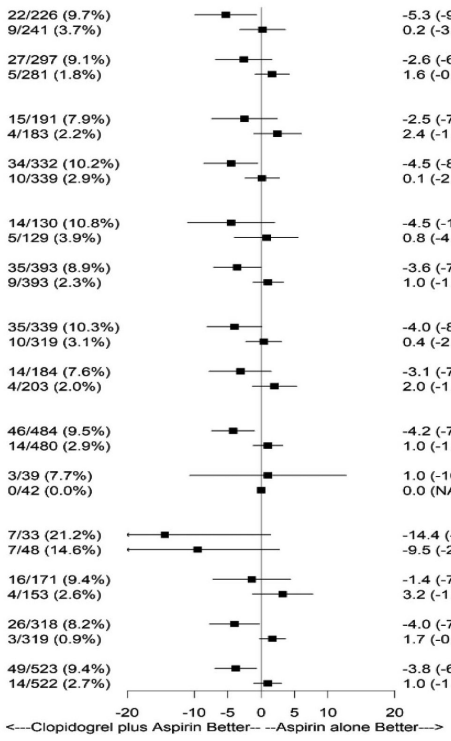
Sensitivity analysis of the population with propensity score matching



Supplementary Figure 3. Distribution of modified Rankin Scale scores at 90 days. The raw distribution of scores is shown (A) across time from symptom onset to antiplatelet therapy, (B) in the 0–24 h time subgroup, and (C) in the 24–48 h time subgroup. The scores ranged from 0 to 6 (0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability; and 6=death).

Subgroup	Clopidogrel plus aspirin	Aspirin alone	RD,% (95% CI)	P Value for trend	P Value for interaction
Age					0.13
Age < 65 years					
0-24h group	11/249 (4.4%)	22/226 (9.7%)	-5.3 (-9.9 to -0.7)	0.02	
24-48h group	10/253 (4.0%)	9/241 (3.7%)	0.2 (-3.2 to 3.6)	0.9	
Age ≥ 65 years					0.1
0-24h group	21/324 (6.5%)	27/297 (9.1%)	-2.6 (-6.8 to 1.6)	0.23	
24-48h group	11/321 (3.4%)	5/281 (1.8%)	1.6 (-0.9 to 4.2)	0.2	
Sex					
Female					0.1
0-24h group	11/205 (5.4%)	15/191 (7.9%)	-2.5 (-7.4 to 2.4)	0.32	
24-48h group	10/216 (4.6%)	4/183 (2.2%)	2.4 (-1.1 to 6.0)	0.17	
Male					0.2
0-24h group	21/368 (5.7%)	34/332 (10.2%)	-4.5 (-8.6 to -0.5)	0.03	
24-48h group	11/358 (3.1%)	10/339 (2.9%)	0.1 (-2.4 to 2.7)	0.92	
History of diabetes					
Yes					0.29
0-24h group	10/159 (6.3%)	14/130 (10.8%)	-4.5 (-11.0 to 2.0)	0.18	
24-48h group	7/150 (4.7%)	5/129 (3.9%)	0.8 (-4.0 to 5.5)	0.74	
No					0.07
0-24h group	22/414 (5.3%)	35/393 (8.9%)	-3.6 (-7.1 to 0.0)	0.047	
24-48h group	14/424 (3.3%)	9/393 (2.3%)	1.0 (-1.2 to 3.3)	0.38	
History of hypertension					
Yes					0.2
0-24h group	22/349 (6.3%)	35/339 (10.3%)	-4.0 (-8.1 to 0.1)	0.06	
24-48h group	13/371 (3.5%)	10/319 (3.1%)	0.4 (-2.3 to 3.0)	0.79	
No					0.09
0-24h group	10/224 (4.5%)	14/184 (7.6%)	-3.1 (-7.8 to 1.5)	0.19	
24-48h group	8/203 (3.9%)	4/203 (2.0%)	2.0 (-1.3 to 5.3)	0.24	
NIHSS score at admission					
4 to 7					0.03
0-24h group	28/527 (5.3%)	46/484 (9.5%)	-4.2 (-7.4 to -1.0)	0.01	
24-48h group	21/535 (3.9%)	14/480 (2.9%)	1.0 (-1.2 to 3.2)	0.38	
8 to 10					0.99
0-24h group	4/46 (8.7%)	3/39 (7.7%)	1.0 (-10.7 to 12.7)	0.87	
24-48h group	0/39 (0.0%)	0/42 (0.0%)	0.0 (NA to NA)		
Presumed stroke cause					
Large artery atherosclerosis					0.89
0-24h group	3/44 (6.8%)	7/33 (21.2%)	-14.4 (-30.2 to 1.4)	0.07	
24-48h group	2/39 (5.1%)	7/48 (14.6%)	-9.5 (-21.6 to 2.7)	0.13	
Small artery occlusion					0.16
0-24h group	15/189 (7.9%)	16/171 (9.4%)	-1.4 (-7.2 to 4.4)	0.63	
24-48h group	9/155 (5.8%)	4/153 (2.6%)	3.2 (-1.3 to 7.7)	0.16	
Undetermined cause					0.02
0-24h group	14/337 (4.2%)	26/318 (8.2%)	-4.0 (-7.7 to -0.3)	0.03	
24-48h group	10/377 (2.7%)	3/319 (0.9%)	1.7 (-0.2 to 3.6)	0.08	
Total					**0.04**
0-24h group	32/573 (5.6%)	49/523 (9.4%)	-3.8 (-6.9 to -0.7)	0.001	
24-48h group	21/574 (3.7%)	14/522 (2.7%)	1.0 (-1.1 to 3.0)	0.36	



Supplementary Figure 4. Subgroup analysis of the effect of antiplatelet therapy on the primary outcome in time subgroups. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. The analysis was not powered and had no pre-specified correction for multiple comparisons for definitive analysis of the subgroups. NIHSS, National Institutes of Health Stroke Scale; RD, risk difference; CI, confidence interval.

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Supplementary Table 4. Baseline characteristics of patients included in the analysis

	0–24 h group				24–48 h group				
	Total patients (n=1,096)	Clopidogrel +aspirin (n=573)	Aspirin alone (n=523)	*P*	Total patients (n=1,096)	Clopidogrel +aspirin (n=574)	Aspirin alone (n=522)	*P*	*P*
Age (yr)	66 (59–73)	66 (59–73)	67 (59–74)	0.29	66 (58–73)	66 (59–73)	65 (58–74)	0.63	0.70
Sex				0.80				0.38	0.89
Male	700 (63.9)	368 (64.2)	332 (63.5)		697 (63.6)	358 (62.4)	339 (64.9)		
Female	396 (36.1)	205 (35.8)	191 (36.5)		399 (36.4)	216 (37.6)	183 (35.1)		
Current smoking	318/1,087 (29.3)	177/568 (31.2)	141/519 (27.2)	0.15	321/1,086 (29.6)	163/568 (28.7)	158/518 (30.5)	0.52	0.88
Current drinking*	186/1,086 (17.1)	107/567 (18.9)	79/519 (15.2)	0.11	197/1,088 (18.1)	96/571 (16.8)	101/517 (19.5)	0.22	0.55
Comorbidities†									
Hypertension	688 (62.8)	349 (60.9)	339 (64.8)	0.18	690 (63.0)	371 (64.6)	319 (61.1)	0.23	0.93
Diabetes	289 (26.4)	159 (27.7)	130 (24.9)	0.28	279 (25.5)	150 (26.1)	129 (24.7)	0.59	0.63
Previous stroke‡	323/1,090 (29.6)	157/568 (27.6)	166/522 (31.8)	0.13	372/1,092 (34.1)	197/572 (34.4)	175/520 (33.7)	0.78	0.03
Previous transient ischemic attack	4/1,088 (0.4)	3/570 (0.5)	1/518 (0.2)	0.36	3/1,091 (0.3)	0/572 (0.0)	3/519 (0.6)	0.07	0.70
Blood pressure at randomization									
Systolic (mm Hg)	154 (140–169)	155 (140–170)	152 (140–168)	0.99	150 (140–167)	150 (140–169)	150 (140–165)	0.69	0.14
Diastolic (mm Hg)	90 (80–98)	90 (80–98)	90 (80–96)	0.30	90 (80–99)	90 (80–100)	90 (80–98)	0.22	0.96
Blood glucose (mmol/L)	6.4 (5.3–9.5)	6.4 (5.4–9.5)	6.3 (5.2–9.5)	0.25	6.5 (5.4–11.5)	6.5 (5.4–11.1)	6.4 (5.3–11.8)	0.57	0.49
NIHSS score at randomization§	4 (4–6)	4 (4–6)	4 (4–6)	0.69	4 (4–6)	4 (4–6)	4 (4–6)	0.56	0.47
Estimated premorbid function (mRS)‖				0.58				0.63	0.91
No symptoms	773 (70.5)	407 (71.0)	366 (70.0)		782 (71.4)	410 (71.4)	372 (71.3)		
Symptoms without disability	322 (29.4)	165 (28.8)	157 (30.0)		313 (28.6)	163 (28.4)	1,500 (28.7)		
Mild disability	1 (0.1)	1 (0.2)	0 (0.0)		1 (0.1)	1 (0.2)	0 (0.00)		
Time from symptom onset to antiplatelet therapy (h)	9.0 (5.5–14.4)	8.9 (5.2–14.1)	9.4 (6.2–14.5)	0.37	28.5 (25.1–41.0)	28.1 (25.0–39.3)	29.0 (25.2–42.3)	0.26	<0.01
Presumed stroke cause¶				0.60				0.32	0.06
Undetermined cause	655 (59.8)	337/573 (58.8)	318/523 (60.8)		696 (63.5)	377 (65.7)	319 (61.1)		
Small artery occlusion	360 (32.8)	189/573 (33.0)	171/523 (32.7)		308 (28.1)	155 (27.0)	153 (29.3)		
Large artery atherosclerosis	77 (7.0)	44/573 (7.7)	33/523 (6.3)		87 (7.9)	39 (6.8)	48 (9.2)		
Other determined cause	2 (0.2)	2/573 (0.3)	0/523 (0.0)		5 (0.5)	3 (0.5)	2 (0.4)		
Cardioembolic	2 (0.2)	1/573 (0.2)	1/523 (0.2)		0 (0.0)	0 (0.0)	0 (0.0)		
Location of responsible vessel				0.11				0.17	0.07
Anterior circulation infarction	694/963 (72.1)	362/512 (70.7)	332/451 (73.6)		639/947 (67.5)	327/502 (65.1)	312/445 (70.1)		
Posterior circulation infarction	239/963 (24.8)	138/512 (27.0)	101/451 (22.4)		279/947 (29.6)	161/502 (32.1)	118/445 (26.5)		
Anterior and posterior circulation infarction	30/963 (3.1)	12/512 (2.3)	18/451 (4.0)		29/947 (3.0)	14/502 (2.8)	15/445 (3.4)		

The data are shown with median (IQR) for continuous characteristics or frequency (percentages) for categorical characteristics.
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; NA, not applicable; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Current drinking means consuming alcohol at least once a week within 1 year before onset of the disease and consuming alcohol continuously for more than 1 year; †The comorbidities were based on the patient or family report; ‡Previous ischemic stroke referred only to the patients with prestroke mRS ≤1; §Patients with NIHSS scores of 6 to 16 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit; ‖Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death). No symptoms indicates scoring 0, symptoms without disability indicates scoring 1, and mild disability indicates scoring 2; ¶The presumed stroke cause was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system[1] using clinical findings, brain imaging, and laboratory tests. Other determined causes included pulmonary embolism, peripheral vessel incident, and cardiovascular incident.

Supplementary Table 5. Association between continuous time from symptom onset and the start antiplatelet therapy with outcomes

	Clopidogrel +aspirin (n=1,147)	Aspirin alone (n=1,045)	Treatment effect metric	Model 1*		Model 2†		Model 3‡		P_{int}
				Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	
Primary outcome										
END§ at 7 days	53/1,147 (4.6)	63/1,045 (6.0)	RD‖	-1.4 (-3.3 to 0.5)	0.14	-1.4 (-2.7 to -0.1)	0.04	-1.4 (-2.7 to -0.1)	0.04	0.17
Secondary outcomes										
mRS¶ 0–1 at 90 days	883/1,125 (78.5)	776/1,042 (76.7)	RD‖	1.8 (-1.7 to 5.4)	0.32	1.8 (-0.7 to 4.3)	0.16	1.8 (-0.7 to 4.3)	0.16	0.90
mRS¶ at 90 days	NA	NA	OR**	1.06 (0.91 to 1.24)	0.46	1.06 (0.95 to 1.19)	0.30	1.06 (0.95 to 1.19)	0.30	0.43
Change in NIHSS†† at 14 days	-0.56 (-0.98 to -0.22)	-0.56 (-1.10 to -0.22)	GMR‖	0.09 (-0.31 to 0.49)	0.66	0.09 (-0.19 to 0.37)	0.54	0.09 (-0.19 to 0.37)	0.54	0.05
New stroke‡‡ within 90 days	10/1,125 (0.9)	11/1,012 (1.1)	HR§§	0.82 (0.35 to 1.93)	0.65	0.83 (0.35 to 1.96)	0.67	0.81 (0.34 to 1.93)	0.64	0.24
Other vascular events‖‖ or death within 90 days	11/1,125 (1.00)	5/1,012 (0.5)	HR§§	1.98 (0.69 to 5.71)	0.20	1.91 (0.66 to 5.49)	0.23	1.77 (0.61 to 5.15)	0.30	0.29
Safety outcomes¶¶										
Any bleeding events	9/1,147 (0.8)	11/1,045 (1.1)	RD‖	-0.3 (-1.1 to 0.5)	0.51	-0.3 (-0.8 to 0.3)	0.36	-0.3 (-0.8 to 0.3)	0.36	0.05
Intracranial hemorrhage	1/1,147 (0.1)	2/1,045 (0.2)	RD‖	-0.1 (-0.4 to 0.2)	0.52	-0.1 (-0.3 to 0.1)	0.36	-0.1 (-0.3 to 0.1)	0.36	0.85

The data are shown with median (IQR) for continuous characteristics or frequency (percentages) for categorical characteristics.
CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RD, risk difference; OR, odds ratio; GMR, geometric mean ratio; HR, hazard ratio; IQR, interquartile range; NA, not applicable; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Unadjusted analysis in the model; †Adjusted for time from symptom onset to antiplatelet therapy in the model; ‡Adjusted for time from symptom onset to antiplatelet therapy and prespecified covariates (age, sex, history of diabetes, history of hypertension, NIHSS score at randomization, and presumed stroke cause based on the TOAST classification[1]); §END was defined as an increase between baseline and 7 days of ≥2 on the NIHSS score, but not as result of cerebral hemorrhage[2]; ‖Calculated using the generalized liner model; ¶Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death); **A shift measures of function according to the full range of scores on the mRS at 90 days was analyzed by ordinal logistic regression, and the chi-square for the likelihood ratio test were 6.0 (*P*=0.31) in the model 1, 12.3 (*P*=0.10) in the model 2, and 12.1 (*P*=0.10) in the model 3; ††Patients with NIHSS scores of 4 to 10 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit. The log(NIHSS+1) was analyzed using generalized linear model; ‡‡New stroke included ischemic stroke and hemorrhagic stroke; §§Calculated using the Cox regression model; ‖‖Other vascular events included pulmonary embolism, peripheral vascular, or cardiovascular event; ¶¶The safety outcomes were analyzed based on the safety analysis set of the ATAMIS trial.

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Supplementary Table 6. Association between categorical time from symptom onset and start antiplatelet therapy with outcomes

	Time	Clopidogrel+aspirin (n=1,147)	Aspirin alone (n=1,045)	Treatment effect metric	Model 1*		Model 4†		Model 5‡		P_{int}
					Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	
Primary outcome											
END§ at 7 days	0–24 h	32/573 (5.6)	49/523 (9.4)	RD‖	-3.8 (-6.9 to -0.7)	0.02	-3.8 (-6.9 to -0.7)	0.02	-4.0 (-6.2 to -1.8)	<0.01	0.03
	24–48 h	21/574 (3.7)	47/522 (2.7)		1.0 (-1.1 to 3.0)	0.36	1.0 (-0.5 to 2.4)	0.20	1.0 (-0.5 to 2.4)	0.20	
Secondary outcomes											
mRS¶ 0–1 at 90 days	0–24 h	418/560 (74.6)	369/505 (73.1)	RD‖	1.6 (-3.7 to 6.9)	0.56	1.6 (-3.7 to 6.9)	0.56	1.6 (-2.1 to 5.3)	0.41	0.95
	24–48 h	465/565 (82.3)	407/507 (80.3)		2.0 (-2.7 to 6.7)	0.40	2.0 (-1.3 to 5.4)	0.23	2.1 (-1.2 to 5.5)	0.21	
mRS¶ at 90 days	0–24 h	NA	NA	OR**	1.11 (0.89 to 1.38)	0.36	1.11 (0.89 to 1.38)	0.36	1.11 (0.95 to 1.30)	0.19	0.19
	24–48 h	NA	NA		1.01 (0.80 to 1.26)	0.96	1.01 (0.86 to 1.18)	0.95	1.01 (0.86 to 1.18)	0.91	
Change in NIHSS†† at 14 days	0–24 h	-0.51 (-0.92 to -0.22)	-0.51 (-0.98 to -0.22)	GMR‖	-0.35 (-0.85 to 0.16)	0.18	-0.35 (-0.85 to 0.16)	0.18	-0.35 (-0.70 to 0.01)	0.06	0.06
	24–48 h	-0.56 (-1.10 to -0.25)	-0.69 (-1.10 to -0.34)		0.53 (-0.09 to 1.14)	0.09	0.53 (0.00 to 0.96)	0.05	0.52 (0.00 to 0.96)	0.05	
New stroke‡‡ within 90 days	0–24 h	3/560 (0.5)	7/505 (1.4)	HR§§	0.52 (0.17 to 1.54)	0.24	0.52 (0.17 to 1.54)	0.24	0.35 (0.09 to 1.38)	0.13	0.10
	24–48 h	7/565 (1.2)	4/507 (0.8)		1.61 (0.47 to 5.50)	0.45	1.57 (0.46 to 5.37)	0.47	1.65 (0.48 to 5.68)	0.47	
Other vascular events‖‖ or death within 90 days	0–24 h	8/560 (1.4)	4/505 (0.8)	HR§§	1.10 (0.49 to 2.46)	0.81	1.10 (0.49 to 2.46)	0.81	1.75 (0.52 to 5.86)	0.36	0.74
	24–48 h	3/565 (0.5)	1/507 (0.2)		2.76 (0.29 to 26.49)	0.38	2.69 (0.28 to 25.87)	0.39	2.05 (0.18 to 23.91)	0.57	
Safety outcomes¶¶											
Any bleeding events	0–24 h	3/573 (0.5)	8/523 (1.5)	RD‖	-1.0 (-2.2 to 0.2)	0.10	-1.0 (-2.2 to 0.2)	0.10	-1.1 (-1.9 to 0.2)	0.10	0.06
	24–48 h	6/574 (1.0)	3/522 (0.6)		0.5 (-0.6 to 1.5)	0.38	0.5 (-0.3 to 1.2)	0.22	0.5 (-0.3 to 1.2)	0.23	
Intracranial hemorrhage	0–24 h	1/573 (0.2)	2/523 (0.4)	RD‖	-0.2 (-0.8 to 0.4)	0.52	-0.2 (-0.8 to 0.4)	0.52	-0.2 (-0.6 to 0.2)	0.36	0.99
	24–48 h	0/574 (0.0)	0/522 (0.0)		NA	NA	NA	NA	NA	NA	

The data are shown with median (IQR) for continuous characteristics or frequency (percentages) for categorical characteristics.

CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RD, risk difference; OR, odds ratio; GMR, geometric mean ratio; HR, hazard ratio; IQR, interquartile range; NA, not applicable; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Unadjusted analysis in the model; †Adjusted for unbalanced covariates between clopidogrel plus aspirin group and aspirin alone group; ‡Adjusted for prespecified covariates (age, sex, history of diabetes, history of hypertension, NIHSS score at randomization, and presumed stroke cause based on the TOAST classification[1]) and unbalanced covariates between clopidogrel plus aspirin group and aspirin alone group; §END was defined as an increase between baseline and 7 days of ≥2 on the NIHSS score, but not as result of cerebral hemorrhage[2]; ‖Calculated using the generalized liner model; ¶Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death); **A shift measures of function according to the full range of scores on the mRS at 90 days was analyzed by ordinal logistic regression, and the chi-square for the likelihood ratio test were 3.38 (*P*=0.64) and 5.25 (*P*=0.39) in the model 1, 3.38 (*P*=0.64) and 10.6 (*P*=0.06) in the model 4, and 6.79 (*P*=0.24) and 9.98 (*P*=0.08) in the model 5; ††Patients with NIHSS scores of 4 to 10 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit. The log(NIHSS+1) was analyzed using generalized linear model; ‡‡New stroke included ischemic stroke and hemorrhagic stroke; §§Calculated using the Cox regression model; ‖‖Other vascular events included pulmonary embolism, peripheral vascular, or cardiovascular event; ¶¶The safety outcomes were analyzed based on the safety analysis set of the ATAMIS trial.

Supplementary Table 7. Sensitivity analysis of the primary outcome with different OTT groupings

Time	END at 7 days, frequency (%)		Treatment effect metric	Model 1		Model 2		Model 3		P_{int}
	Clopidogrel +aspirin (n=1,502)	Aspirin alone (n=1,413)		Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	Treatment difference (95% CI)	*P*	
Two categories										0.09
0–18 h	45/762 (5.9)	68/710 (9.6)	RD	-3.7 (-6.4 to -0.9)	<0.01	-4.0 (-6.9 to -1.1)	<0.01	-3.5 (-6.5 to -0.6)	0.02	
18–48 h	27/740 (3.6)	27/703 (3.8)		-0.2 (-2.2 to 1.8)	0.85	-0.2 (-2.2 to 1.8)	0.85	0.0 (-1.8 to 1.9)	0.98	
Three categories										0.17
0–12 h	33/592 (5.6)	56/555 (10.1)	RD	-4.5 (-7.6 to -1.4)	<0.01	-3.8 (-7.1 to -0.6)	0.02	-4.8 (-7.9 to -1.7)	<0.01	
12–36 h	38/729 (5.2)	34/645 (5.3)		-0.1 (-2.4 to 2.3)	0.96	-0.1 (-2.5 to 2.3)	0.95	0.0 (-2.4 to 2.5)	0.97	
36–48 h	1/181 (0.6)	5/213 (2.3)		-1.8 (-4.1 to 0.5)	0.13	-2.1 (-3.5 to 0.0)	0.05	-1.7 (-3.4 to 0.0)	0.06	
Four categories										0.07
0–12 h	33/592 (5.6)	56/555 (10.1)	RD	-4.5 (-7.6 to -1.4)	<0.01	-3.8 (-7.1 to -0.6)	0.02	-4.8 (-7.9 to -1.7)	<0.01	
12–24 h	18/310 (5.8)	23/300 (7.7)		-1.9 (-5.8 to 2.1)	0.36	-1.9 (-5.8 to 2.1)	0.36	-1.9 (-5.8 to 2.1)	0.36	
24–36 h	20/419 (4.8)	11/345 (3.2)		1.6 (-1.2 to 4.3)	0.26	1.7 (-1.2 to 4.7)	0.25	1.8 (-0.1 to 3.7)	0.06	
36–48 h	1/181 (0.6)	5/213 (2.3)		-1.8 (-4.1 to 0.5)	0.13	-2.1 (-3.5 to 0.0)	0.05	-1.7 (-3.4 to 0.0)	0.06	

OTT, time from stroke onset to antiplatelet therapy; CI, confidence interval; END, early neurological deterioration; RD, risk difference.

Supplementary References

1. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41.
2. Yi X, Zhou Q, Wang C, Lin J, Chai Z. Aspirin plus clopidogrel may reduce the risk of early neurologic deterioration in ischemic stroke patients carrying CYP2C19*2 reduced-function alleles. *J Neurol* 2018;265:2396-2403.

 https://doi.org/10.5853/jos.2024.02250