Supplementary methods

The PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage for reducing COGnitive decline (PICASSO-COG) substudy was conducted only in South Korea (59 centers) because the cognitive assessment tools had not been validated by cross-cultural studies in each language.

The primary outcome was the change in Mini-Mental State Examination (MMSE) score over time from baseline in an intention-to-treat population. A restricted maximum likelihood-based mixed effects model with repeated measurements (MMRM) was used to compare cognitive changes over time between groups. The model included the fixed categorical effects of treatment group and sex as well as fixed continuous covariates of the patient's age, duration of education, number of visits, baseline cognitive scores, and the National Institutes of Health Stroke Scale (NIHSS) score. The effect of the study sites was adjusted as a random factor in the model. An unstructured covariance structure, common to the treatments, was used to model the within-subject correlation. Although this study had a 2×2 factorial design, the efficacy of each treatment was analyzed separately because the interaction effect between the antiplatelets and lipid-lowering treatment was not significant.

As cognitive impairment is an independent risk factor for attrition in a longitudinal study, we performed sensitivity analysis to examine its influence on cognitive outcome. Sensitivity analyses included the following: (1) a restricted maximum likelihood-based MMRM analysis with further adjustment for the participant's drop-out status during the trial period as well as treatment status at the previous visit, which is defined as the patient missing the cognitive evaluation in the scheduled visit before the current visit, in the model; (2) MMRM analyses of participants' cognitive evaluation at baseline and follow-up visits at 13, 25, 37, and 49 months; (3) MMRM analyses of participants who completed all scheduled visits during the following periods: baseline to 13 months, baseline to 25 months, baseline to 37 months, and baseline to 49 months; and (4) MMRM analyses of participants with ischemic stroke as an entry event excluding transient ischemic attack.

The primary outcome between the comparative arms was compared for the following subgroups: diabetes versus non-diabetes, mild to moderate (Fazekas grade 0–2) versus severe (Fazekas grade 3) white matter hyperintensities on magnetic resonance imaging, baseline MMSE ≤24 versus >24, and concomitant use of statin versus non-use. The same analyses as performed in the sensitivity and subgroup analyses were reconducted in the propensity score matched subsets, which were constructed using the variables of subject age, sex, educational years, baseline cognitive score, and baseline NIHSS score to overcome the differences between the treatment groups arising from non-random missing in this substudy.

The longitudinal change in MoCA was also evaluated using the same statistical methods. A two-sided *P*-value of 0.05 was used to indicate statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Supplementary Table 1. Baseline characteristics of the included and excluded subjects

Characteristic	PICASSO-COG study			MMSE analysis			MoCA analysis		
	Included (n=1,240)	Excluded (n=142)	*P*	Included (n=892)	Excluded (n=348)	*P*	Included (n=877)	Excluded (n=363)	*P*
Age (yr)	65.8±10.8	68.3±10.0	0.01	64.9±10.8	68.2±10.5	<0.01	64.8±10.8	68.3±10.4	<0.01
Female sex	480 (38.7)	53 (37.3)	0.75	327 (36.7)	153 (44.0)	0.02	318 (36.3)	162 (44.6)	0.01
Education (yr)	9 (6–12)	9 (6–12)	0.41	9 (6–12)	6 (5–12)	<0.01	9 (6–12)	6 (5–12)	<0.01
Hypertension	1,091 (88.0)	133 (93.7)	0.04	796 (89.2)	295 (84.8)	0.03	783 (89.3)	308 (84.9)	0.03
Diabetes	389 (31.4)	53 (37.3)	0.15	276 (30.9)	113 (32.5)	0.60	271 (30.9)	118 (32.5)	0.58
Hyperlipidemia	511 (41.2)	54 (38.0)	0.47	373 (41.8)	138 (40.0)	0.49	369 (42.1)	142 (39.1)	0.34
Use of lipid-lowering agent*	969 (78.2)	85 (59.9)	<0.01	695 (77.9)	274 (78.7)	0.75	686 (78.2)	283 (78.0)	0.92
Coronary artery disease	59 (4.8)	8 (5.6)	0.65	37 (4.2)	22 (6.3)	0.11	37 (4.2)	22 (6.1)	0.17
Smoking	546 (44.0)	65 (45.8)	0.69	407 (45.6)	139 (39.9)	0.07	404 (46.1)	142 (39.1)	0.02
Index event			0.01			0.18			0.05
Ischemic stroke	1,175 (94.8)	142 (100.0)		850 (95.3)	325 (93.4)		838 (95.6)	337 (92.8)	
Transient ischemic attack	65 (5.2)	0 (0.0)		42 (4.7)	23 (6.6)		39 (4.5)	26 (7.2)	
Baseline NIHSS	1 (0–3)	3 (1-5)	<0.01	1 (0–3)	2 (1–4)	<0.01	1 (0–3)	2 (1–4)	<0.01
Baseline MMSE	26 (21–28)	-	-	26 (23–29)	24 (17–27)	<0.01	26 (23–29)	24 (17–27)	<0.01
24 or less	492 (39.7)	-		313 (35.1)	179 (51.4)	<0.01	303 (34.6)	189 (52.1)	<0.01
>24	748 (60.3)	-		579 (64.9)	169 (48.6)		574 (65.4)	174 (47.9)	
Baseline MoCA	20 (14–24)	-	-	20 (16–24)	17 (10–22)	<0.01	20 (16–24)	17 (10–22)	<0.01
Treatment									
Cilostazol	618 (49.8)	71 (50.0)	0.97	451 (50.6)	167 (48.0)	0.42	447 (51.0)	171 (47.1)	0.22
Probucol	622 (50.2)	69 (48.6)	0.72	459 (51.5)	163 (46.8)	0.14	452 (51.5)	170 (46.8)	0.13
SBP (mm Hg)	135.4±18.4	133.7±19.1	0.30	135.4±18.6	135.5±17.8	0.96	135.3±18.7	135.6±17.6	0.79
DBP (mm Hg)	80.1±11.8	80.9±12.2	0.43	80.1±11.8	80.2±11.8	0.88	80.1±11.9	80.2±11.6	0.85
BP readings	7 (4–13)	10 (3–18)	0.01	9 (6–13)	2 (1–4)	<0.01	9 (6–13)	2 (1–4)	<0.01
Follow-up periods (yr)	1.9 (1.0–3.0)	2.7 (0.6–4.5)	<0.01	2.1 (1.3–3.0)	0.5 (0.1–1.1)	<0.01	2.1 (1.3–3.0)	0.6 (0.1–1.1)	<0.01
Severe WMH	324 (27.1)	30 (22.1)	0.21	210 (24.5)	114 (33.5)	<0.01	206 (24.4)	118 (33.2)	<0.01
Outcome events									
Recurrent stroke†	102 (8.2)	9 (6.3)	0.43	44 (4.9)	58 (16.7)	<0.01	41 (4.7)	61 (16.8)	<0.01
Ischemic	80 (6.5)	8 (5.6)	0.71	31 (3.5)	49 (14.1)	<0.01	30 (3.4)	50 (13.8)	<0.01
Hemorrhagic	23 (1.9)	1 (0.7)	0.50	14 (1.6)	9 (2.6)	0.23	12 (1.4)	11 (3.0)	0.048
Myocardial infarction	8 (0.7)	1 (0.7)	0.99	3 (0.3)	5 (1.4)	0.04	3 (0.3)	5 (1.4)	0.04
Death	39 (3.2)	9 (6.3)	0.08	17 (1.9)	22 (6.3)	<0.01	17 (1.9)	22 (6.1)	<0.01

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Severe white matter hyperintensities were defined as Fazekas grade 3.

PICASSO-COG, PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage for reducing COGnitive decline; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; WMH, white matter hyperintensity.

*Prior to randomization; †One subject had both ischemic and hemorrhagic stroke and was counted as a duplicate.

https://doi.org/10.5853//jos.2020.03650

Supplementary Table 2. Baseline characteristics of the study subjects

Characteristic	Antiplatelet treatment		Lipid-lowering treatment	
	Cilostazol (n=451)	Aspirin (n=441)	Probucol (n=459)	No probucol (n=433)
Age (yr)	65.0±10.8	64.8±10.8	64.7±10.8	65.2±10.8
Male sex	283 (62.7)	282 (63.9)	290 (63.2)	275 (63.5)
Education (yr)	9 (6–12)	9 (6–12)	9 (6–12)	9 (6–12)
Entry event				
Ischemic stroke	432 (95.8)	418 (94.8)	441 (96.1)	409 (94.5)
Transient ischemic attack	19 (4.2)	23 (5.2)	18 (3.9)	24 (5.5)
Index of high risk of ICH				
Prior history of ICH	69 (15.3)	76 (17.2)	72 (15.7)	73 (16.9)
Imaging findings of ICH without clinical history	83 (18.4)	77 (17.5)	87 (18.9)	73 (16.9)
Multiple microbleeds (≥2)	299 (66.3)	288 (65.3)	300 (65.4)	287 (66.3)
Time-to-randomization since entry event (day)	18 (9–41)	18 (9–42)	18 (9–43)	18 (8–41)
≤10	130 (28.8)	132 (29.9)	128 (27.9)	134 (30.9)
11–30	177 (39.2)	173 (39.2)	180 (39.2)	170 (39.3)
31–90	93 (20.6)	93 (21.1)	95 (20.7)	91 (21.0)
>90	51 (11.3)	43 (9.8)	56 (12.2)	38 (8.8)
Baseline NIHSS	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
Baseline MMSE	26 (22–28)	27 (23–29)	26 (22–28)	26 (23–29)
Baseline MMSE ≤24	173 (38.4)	140 (31.7)	160 (34.9)	153 (35.3)
Baseline MoCA	20 (15–24)	21 (16–24)	20 (15.5–24)	21 (16–24)
Time-to-baseline MMSE since entry event (day)	136 (125–148)	135 (127–151)	136 (126–151)	135 (127–148.5)
Risk factors				
Hypertension	402 (89.1)	394 (89.3)	411 (89.5)	385 (88.9)
Diabetes mellitus	134 (29.7)	142 (32.2)	136 (29.6)	140 (32.3)
Dyslipidemia	183 (40.6)	190 (43.1)	206 (44.9)	167 (38.6)
Current smoking	93 (20.6)	102 (23.1)	103 (22.4)	92 (21.2)
Coronary artery disease	15 (3.3)	22 (5.0)	22 (4.8)	15 (3.5)
Lipids (mg/dL)				
Total cholesterol	165.7±39.2	169.0±41.1	170.5±40.8	164.0±39.3
LDL-C	101.0±36.0	102.7±35.4	104.7±36.4	98.7±34.7
HDL-C	45.2±11.7	45.9±12.1	45.5±12.1	45.5±11.7
Fazekas score for WMH				
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	122 (27.1)	141 (32.0)	130 (29.1)	133 (32.4)
2	194 (43.0)	191 (43.3)	213 (47.6)	172 (41.8)
3	112 (24.8)	98 (22.2)	104 (23.3)	106 (25.8)
Concomitant therapy				
Aspirin (after randomization)			218 (47.5)	223 (51.5)
Cilostazol (after randomization)			241 (52.5)	210 (48.5)
Probucol	241 (53.4)	218 (49.4)		
Other lipid-lowering agents	355 (79.1)	353 (80.2)	360 (78.8)	348 (80.6)

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WMH, white matter hyperintensity.

Supplementary Table 3. MMRM analysis in cilostazol vs. aspirin and probucol vs. no probucol groups

Time point	Cilostazol vs. aspirin						Probucol vs. no probucol					
	MMSE			MoCA			MMSE			MoCA		
	Cilostazol (n=451)	Aspirin (n=441)	*P*	Cilostazol (n=447)	Aspirin (n=430)	*P*	Probucol (n=459)	No probucol (n=433)	*P*	Probucol (n=452)	No probucol (n=425)	*P*
Baseline	24.76±4.48	25.07±4.89	0.81*	18.98±6.16	19.67±6.31	0.31*	24.93±4.73	24.90±4.65	0.57*	19.23±6.15	19.42±6.33	0.01*
1st Follow-up	24.85±4.65	25.10±4.95	<0.01†	19.02±6.37	19.78±6.62	0.045†	25.00±5.03	24.94±4.55	<0.01†	19.44±6.43	19.34±6.58	0.03†
2nd Follow-up	24.61±5.12	25.13±4.92		18.75±6.66	19.91±6.57		24.91±5.03	24.83±5.03		19.31±6.81	19.33±6.46	
3rd Follow-up	24.56±5.29	24.82±5.35		19.01±6.80	19.43±6.96		24.81±5.17	24.54±5.48		19.67±6.72	18.69±7.04	
4th Follow-up	23.97±5.51	25.15±5.41		18.69±7.34	20.62±6.98		24.41±5.69	24.84±5.17		19.91±7.48	19.36±6.82	

Values are presented as mean±standard deviation. *P*-values for treatment-by-time interaction were not significant in any analysis.
MMRM, maximum likelihood-based mixed effects model with repeated measurements; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.
**P*-value for MMRM for treatment effect; †*P*-value for MMRM for the time effect.

https://doi.org/10.5853//jos.2020.03650

Supplementary Table 4. Subgroup analysis of the cilosatzol/aspirin groups and probucol/no probucol groups

Variable	Baseline	1st Follow-up	2nd Follow-up	3rd Follow-up	4th Follow-up
Cilosatzol/aspirin MMSE scores					
Baseline MMSE ≤24 (n=313)					
Cilostazol (n=173)	20.10±3.56	20.70±4.52	19.84±5.03	19.94±5.26	19.40±5.21
Aspirin (n=140)	19.23±4.41	19.73±5.10	20.01±5.44	19.67±5.90	16.54±6.15
P	0.83*	0.01†			
Baseline MMSE >24 (n=579)					
Cilostazol (n=278)	27.66±1.65	27.41±2.30	27.28±2.62	27.40±2.64	26.76±3.46
Aspirin (n=301)	27.79±1.65	27.56±2.14	27.34±2.39	27.26±2.67	27.26±2.16
P	0.82*	0.01†			
Probucol/no probucol MoCA scores					
Diabetes mellitus (n=271)					
Probucol (n=135)	18.70±6.29	18.68±6.61	18.17±6.80	18.16±6.85	18.59±8.46
No probucol (n=136)	18.82±6.06	18.71±6.14	18.52±6.00	17.72±6.28	18.05±6.76
P	0.16*	0.18†			
No diabetes mellitus (n=606)					
Probucol (n=317)	19.45±6.09	19.77±6.34	19.77±6.78	20.19±6.61	20.28±7.22
No probucol (n=289)	19.70±6.45	19.63±6.77	19.72±6.65	19.21±7.40	20.24±6.82
P	0.02*	0.01†			
Concomitant lipid-lowering agents (n=699)					
Probucol (n=355)	19.46±6.08	19.73±6.28	19.81±6.60	20.06±6.51	20.69±7.19
No probucol (n=344)	19.47±6.35	19.44±6.62	19.59±6.38	19.23±6.70	19.45±6.73
P	0.08*	0.38†			
No concomitant lipid-lowering agents (n=175)					
Probucol (n=95)	18.35±6.41	18.44±6.94	17.71±7.30	18.58±7.28	17.06±8.23
No probucol (n=80)	19.21±6.34	18.84±6.46	18.30±6.75	16.62±7.95	19.13±7.30
P	0.03*	0.03†			
Baseline MMSE ≤24 (n=303)					
Probucol (n=155)	12.94±4.90	12.90±5.11	12.60±5.79	13.21±5.82	11.92±6.41
No probucol (n=148)	12.86±5.10	12.78±5.13	12.17±4.89	11.61±5.64	8.55±5.43
P	0.18*	<0.01†			
Baseline MMSE >24 (n=574)					
Probucol (n=297)	22.51±3.69	22.78±4.03	22.75±4.26	23.14±4.10	23.75±4.22
No probucol (n=277)	22.92±3.52	22.82±4.17	22.55±4.05	22.42±4.30	22.07±3.77
P	0.01*	0.88†			
Mild to moderate white matter hyperintensities (n=637)					
Probucol (n=338)	20.37±5.51	20.75±5.86	20.70±6.10	20.97±5.95	21.42±6.42
No probucol (n=299)	20.48±5.91	20.43±6.15	20.47±5.76	20.16±6.10	20.85±5.28
P	<0.01*	0.40†			
Severe white matter hyperintensities (n=206)					
Probucol (n=102)	15.49±6.58	15.18±6.44	14.69±7.06	15.35±7.41	14.20±8.85
No probucol (n=104)	16.35±6.61	16.03±6.82	15.99±7.24	14.05±7.87	15.30±9.29
P	0.79*	0.01†			

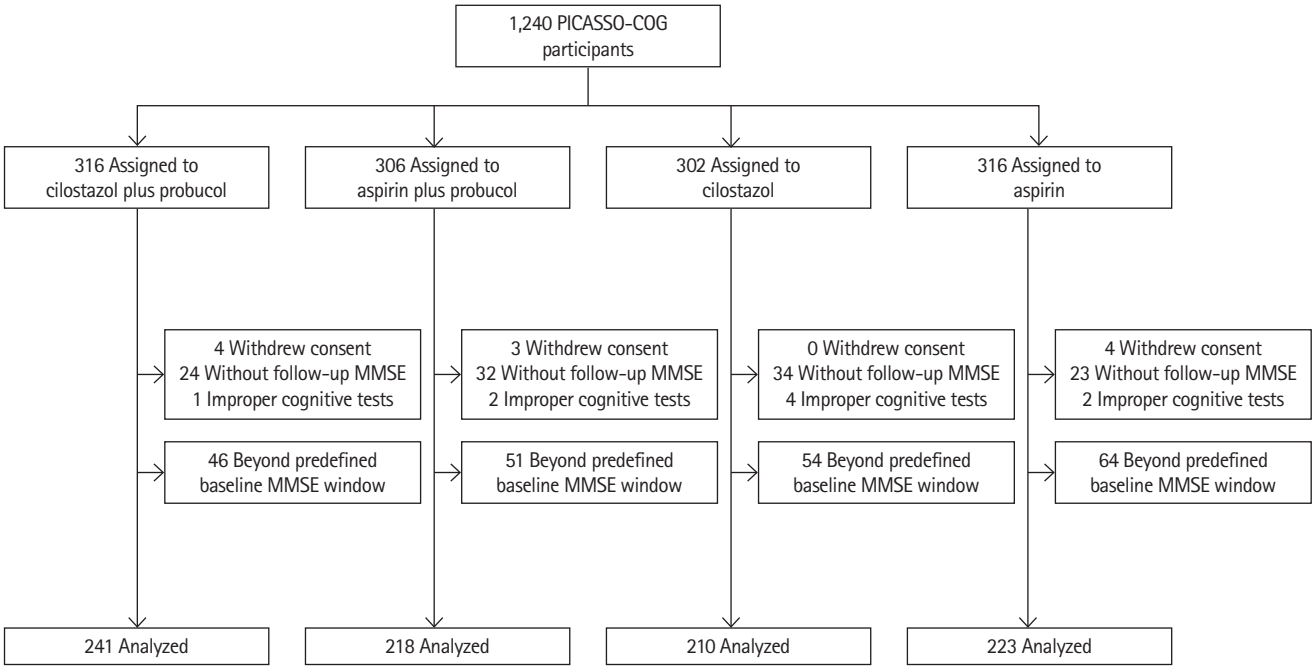
Values are presented as mean±standard deviation. Mild to moderate white matter hyperintensities were defined as Fazekas grade 1 or 2, and severe white matter hyperintensities as Fazekas grade 3. *P*-values for treatment by time interactions were not significant for any analysis.
MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.
**P*-value by MMRM for the treatment effect; †*P*-value by MMRM for the time effect.

Supplementary Table 5. Comparisons of MMSE scores between cilostazol and aspirin group according to severity of white matter changes in propensity score matched subsets

MMSE scores	Mild to moderate white matter hyperintensities (n=574)			Severe white matter hyperintensities (n=148)		
	Cilostazol (n=287)	Aspirin (n=287)	*P*	Cilostazol (n=74)	Aspirin (n=74)	*P*
Baseline	25.85±3.79	25.85±4.25	0.02*	22.66±4.69	22.27±6.01	0.12*
1st Follow-up	26.14±3.59	25.99±4.36	0.26†	21.95±5.36	22.01±5.72	<0.01†
2nd Follow-up	26.08±3.99	25.83±4.05		21.79±5.85	21.74±6.81	
3rd Follow-up	26.43±3.30	25.47±4.63		20.03±6.53	21.47±7.16	
4th Follow-up	26.30±3.06	25.75±5.18		16.90±6.87	20.73±7.04	

Values are presented as mean±standard deviation. The propensity score was calculated using variables, including the participant's age, sex, duration of education, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline MMSE score, baseline Montreal Cognitive Assessment (MoCA) score, coronary artery disease (yes/no), hypertension (yes/no), systolic blood pressure, and pattern of measurement within each white matter hyperintensity. Mild to moderate white matter hyperintensities were defined as Fazekas grade 1 or 2, and severe white matter hyperintensities as Fazekas grade 3. *P*-values for treatment by time interactions were not significant for any analysis.
MMSE, Mini-Mental State Examination.
**P*-value by MMRM for the treatment effect; †*P*-value by MMRM for the time effect.

https://doi.org/10.5853//jos.2020.03650



Supplementary Figure 1. Flow diagram of subject enrollment. PICASSO-COG, PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage for reducing COGnitive decline; MMSE, Mini-Mental State Examination.