

ONLINE SUPPLEMENTS

Title: Comparative effectiveness of combined antiplatelet treatments in acute minor ischemic stroke

Supplemental Methods

Supplemental Figure 2

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Supplemental Methods

(A) Statistical analysis

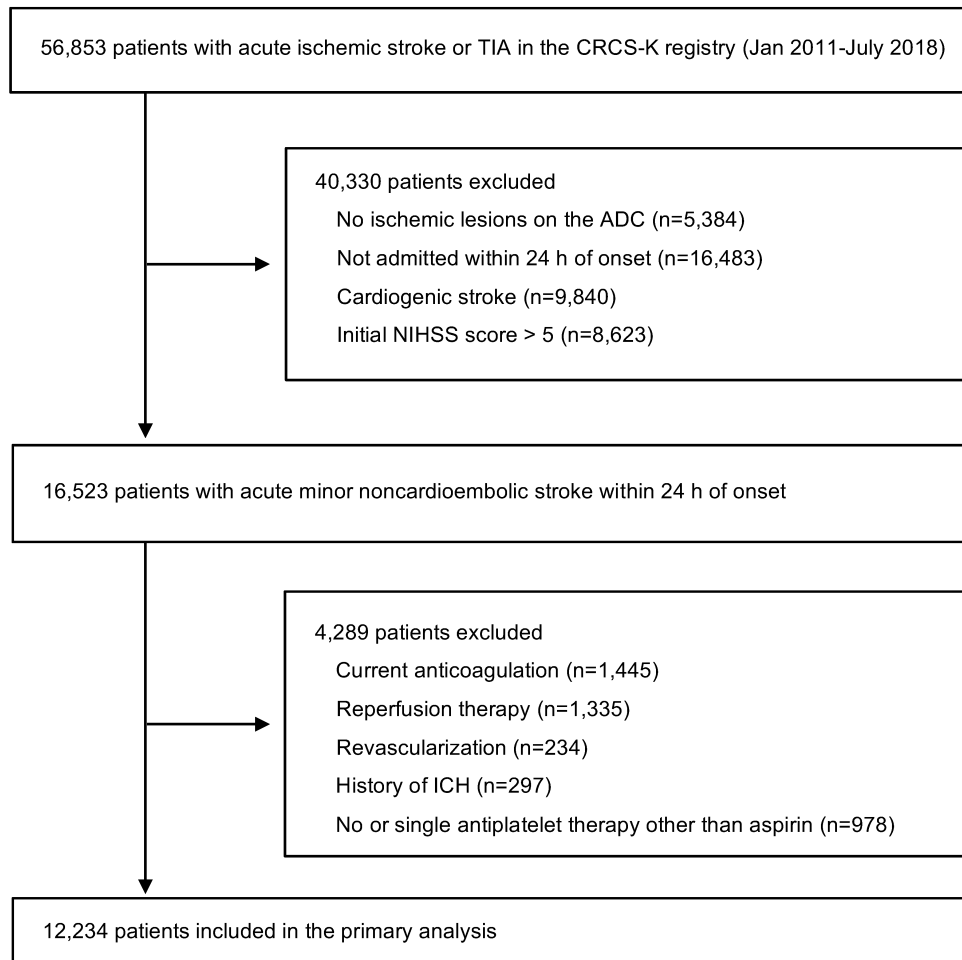
Frequencies (percentages), means (SDs), and medians (interquartile ranges, IQRs) were reported depending on the variable type. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test, and continuous variables were analyzed using Student's t-test or the Wilcoxon rank-sum test, as appropriate. The following parameters had missing data that were substituted using median values: white blood cell count (0.1%), creatinine (1.0% of the data were missing), initial random glucose (0.7%), hemoglobin (0.1%), platelet count (0.2%), and first fasting LDL cholesterol (3.1%).

To minimize confounding and residual selection bias in observational treatment comparisons, a propensity score weighting method was applied to control for imbalances in various baseline characteristics across the three groups. In this study, a generalized propensity score was applied using multinomial logistic regression, and the corresponding inverse probabilities of treatment weights (the reciprocals of the propensity scores) were estimated.

To evaluate the effects of clopidogrel-aspirin or aspirin alone compared with other combination treatments and other covariates on various outcomes, hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using weighted Cox proportional hazards regression models with inverse probability of treatment weighting (IPTW) and robust standard errors. The event rates of the primary and secondary outcome measures were estimated using adjusted Kaplan-Meier estimates and compared using the IPTW log-rank test.⁵

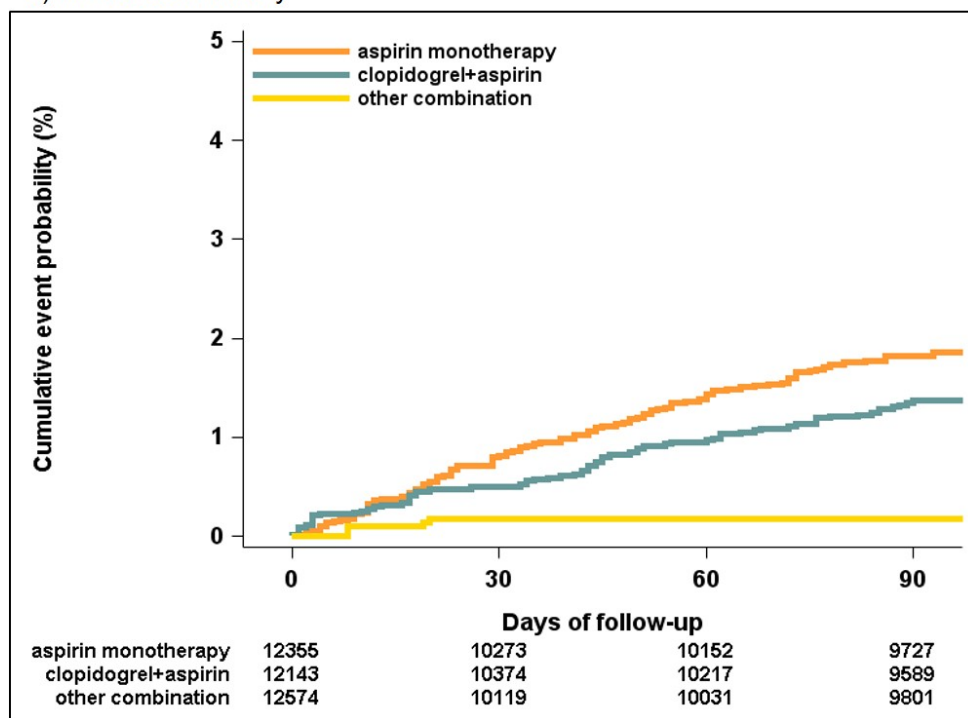
Supplemental analyses were performed using Cox proportional hazard models with adjustment for variables that were predetermined based on their influence on the outcomes and treatment groups (i.e., age; male sex; initial NIHSS score; arrival time; TOAST classification; TIA history, stroke, CAD, or PAD; HTN; DM; dyslipidemia; smoking; atrial fibrillation; prior antiplatelet, antihypertensive, antidiabetic, statin, or lipid-lowering agent use; multiple lesions; LASO; discharge medications including antihypertensives, antidiabetics, statins, and lipid-lowering agents; creatinine; hemoglobin; platelet count; LDL-C; glucose; and SBP).

Supplemental Figure 1. Selection of the study population

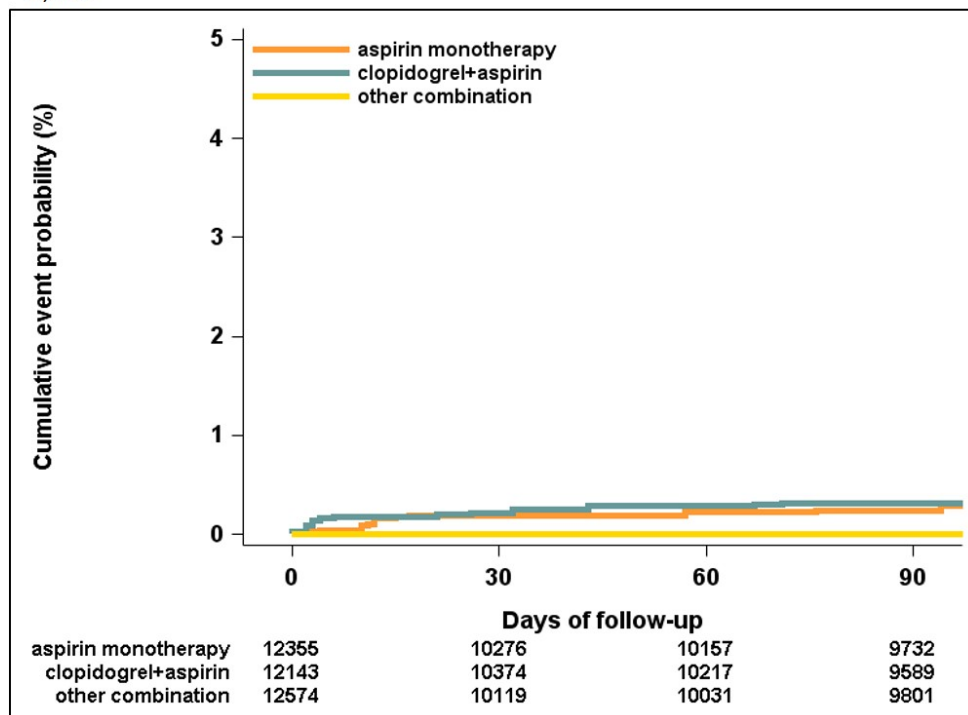


Supplemental Figure 2. Weighted Kaplan-Meier incidence plots for all-cause mortality (a) and MI (b) in patients treated with other combined antiplatelets, clopidogrel-aspirin, and aspirin monotherapy.

a) All-cause mortality



b) MI



Supplemental Table 1. Detailed antiplatelet regimens (A) and protocols (B)

(A) Detailed antiplatelet regimens

	N	%	% within groups
Aspirin monotherapy	6391	52.2	
Clopidogrel + Aspirin	5243	42.9	
Other combined treatment	600	4.9	
Cilostazol + Aspirin	403	3.3	67.2
Cilostazol + Clopidogrel	51	0.4	8.5
Cilostazol + Ticlopidine	1	0.0	0.2
Cilostazol + Triflusal	1	0.0	0.2
Ticlopidine + Aspirin	36	0.3	6.0
Ticlopidine + Triflusal	1	0.0	0.2
Triflusal + Aspirin	5	0.0	0.8
Triflusal + Clopidogrel	5	0.0	0.8
Triple or more combination	97	0.8	16.2
Cilostazol + Aspirin + Clopidogrel	91		
Ticlopidine+ Aspirin + Clopidogrel	4		
Triflusal + Aspirin + Clopidogrel	2		
Total	12234		

(B) Antiplatelet protocols

Antiplatelet regimens	Loading dose	Maintain dose	Duration
Aspirin	100-300mg	100mg	
Clopidogrel	75-300mg	75mg	
Cilostazol	100-200mg	50-200mg	
Triflusal	600-900mg	600-900mg	
Ticlopidine	200-500mg	200-500mg	
Clopidogrel + Aspirin			within 3 months*
Other combination			within 3 months*

*Some patients are allowed to 3 months or more (up to 1 year).

Supplemental Table 2. Propensity score analysis

	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	ASD1	ASD2
N	12355	12143	12574		
Age (yrs.), mean (SD)	65.7 (18.1)	65.7 (19.4)	66.7 (56.0)	0.025	0.024
Male, n (%)	7623 (61.7)	7511 (61.9)	7750 (61.6)	0.001	0.004
Onset-to-admission time				0.005	0.005
Within 12 h	9204 (74.5)	9049 (74.5)	9396 (74.7)		
12 h-24 h	3151 (25.5)	3093 (25.5)	3178 (25.3)		
Body mass index, mean (SD)	24.0 (4.5)	23.9 (5.0)	23.9 (15.1)	0.008	0.006
NIHSS score, median (IQR)	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	0.005	0.006
TOAST				0.093	0.075
LAA	5338 (43.2)	5244 (43.2)	5398 (42.9)		
SVO	3889 (31.5)	3831 (31.5)	4238 (33.7)		
OE	406 (3.3)	411 (3.4)	302 (2.4)		
UD	2722 (22.0)	2657 (21.9)	2636 (21.0)		
History of TIA	309 (2.5)	291 (2.4)	289 (2.3)	0.013	0.006
History of stroke	1979 (16.0)	1941 (16.0)	1779 (14.1)	0.052	0.051
History of PAD	59 (0.5)	46 (0.4)	40 (0.3)	0.025	0.010
History of CAD	873 (7.1)	825 (6.8)	705 (5.6)	0.060	0.049
Hypertension	8053 (65.2)	7880 (64.9)	8494 (67.5)	0.050	0.056
Diabetes mellitus	4023 (32.6)	3946 (32.5)	3866 (30.7)	0.039	0.038
Dyslipidemia	3788 (30.7)	3821 (31.5)	3670 (29.2)	0.032	0.050
Smoking status				0.070	0.101
Never smoker	7226 (58.5)	7061 (58.1)	7295 (58.0)		
Ex-smoker, >5 yrs.	1021 (8.3)	1034 (8.5)	937 (7.5)		
Recent smoker, within 5 yrs.	617 (5.0)	620 (5.1)	504 (4.0)		
Current smoker	3490 (28.2)	3427 (28.2)	3838 (30.5)		
Atrial fibrillation	91 (0.7)	69 (0.6)	56 (0.4)	0.038	0.017
Prior antiplatelet use	3126 (25.3)	3008 (24.8)	2897 (23.0)	0.053	0.041
Prior antihypertensive use	5854 (47.4)	5728 (47.2)	6025 (47.9)	0.011	0.015
Prior statin use	2181 (17.7)	2156 (17.8)	1957 (15.6)	0.056	0.059
Prior lipid-lowering agent use	257 (2.1)	242 (2.0)	199 (1.6)	0.037	0.031
Prior antidiabetic use	2976 (24.1)	2915 (24.0)	2822 (22.4)	0.039	0.037
Multiple lesions	1357 (11.0)	1293 (10.6)	1271 (10.1)	0.029	0.018
LASO				0.030	0.000
No stenosis	7094 (57.4)	7001 (57.7)	7302 (58.1)		
Mild (<50%)	1249 (10.1)	1215 (10.0)	1308 (10.4)		
Significant (≥50%)	2385 (19.3)	2361 (19.4)	2406 (19.1)		
Occlusion	1627 (13.2)	1565 (12.9)	1559 (12.4)		
In-hospital treatment					
Antidiabetics	3034 (24.6)	2978 (24.5)	3243 (25.8)	0.029	0.029
Antihypertensives	5276 (42.7)	5144 (42.4)	5678 (45.2)	0.049	0.056
Anti-lipid lowering agents	7768 (62.9)	7634 (62.9)	7812 (62.1)	0.015	0.015
Statins	11332 (91.7)	11161 (91.9)	11482 (91.3)	0.014	0.022
Laboratory findings, mean (SD)					
WBC count	8.0 (3.9)	8.0 (4.3)	7.9 (13.2)	0.010	0.009
Creatinine	1.02 (1.62)	1.00 (1.30)	0.99 (4.06)	0.011	0.003
Hemoglobin	13.8 (2.7)	13.8 (2.8)	13.8 (8.1)	0.001	0.002
Platelet count	235.2 (96.4)	235.0 (102.1)	234.5 (320.0)	0.003	0.002

LDL-cholesterol	111.1 (50.4)	111.4 (56.3)	112.9 (175.3)	0.013	0.011
Glucose	144.6 (87.8)	144.6 (94.4)	142.2 (276.3)	0.012	0.012
Systolic blood pressure	150.1 (38.6)	150.5 (41.6)	151.8 (128.7)	0.018	0.014

ASD: absolute standardized difference.

*An ASD >0.1 is considered a meaningful imbalance.

Supplemental Table 3. Crude event rates according to antiplatelet treatment

	aspirin monotherapy		clopidogrel-aspirin		other combination		P [†]	AM vs other	C-A vs other
	No. of events	3-month event rate (%; 95% CI) ^a	No. of events	3-month event rate (%; 95% CI) ^a	No. of events	3-month event rate (%; 95% CI) ^a		P1 [‡]	P2 [‡]
Primary outcome; composite of all strokes, MI, and all-cause mortality	941	14.71 (13.83-15.58)	698	13.39 (12.46-14.32)	89	15.01 (12.13-17.89)	0.082	0.295	0.066
Secondary outcome									
All strokes	875	13.64 (12.80-14.49)	651	12.47 (11.57-13.37)	87	14.67 (11.82-17.52)	0.077	0.556	0.049
All-cause mortality	93	1.67 (1.33-2.01)	68	1.50 (1.15-1.85)	3	0.60 (0.00-1.27)	0.151	0.195	1.000
MI	10	0.16 (0.06-0.27)	14	0.30 (0.14-0.45)	0	0.00 (0.00-0.00)	0.230	1.000	0.178

^a Based on the Kaplan-Meier estimates.

[†] P-value by the log-rank test.

[‡] Adjusted P-value by the Bonferroni adjustment method.

Supplemental Table 4. Propensity score analysis of sensitivity analysis for the cilostazol-based combination

	Before multiple treatment PS					After multiple treatment PS				
	Aspirin monotherapy	Clopidogrel-aspirin	Cilostazol-based combination	ASD1	ASD2	Aspirin monotherapy	Clopidogrel-aspirin	Cilostazol-based combination	ASD1	ASD2
N	6391	5243	547			12297	12091	12570		
Age (yrs.), mean (SD)	64.3 (13.4)	66.7 (12.5)	67.9 (11.5)	0.289	0.103	65.6 (18.1)	65.6 (19.4)	66.7 (59.8)	0.024	0.023
Male, n (%)	3938 (61.6)	3281 (62.6)	315 (57.6)	0.082	0.102	7585 (61.7)	7477 (61.8)	7719 (61.4)	0.006	0.009
Onset-to-admission time				0.037	0.002				0.004	0.003
Within 12 h	4710 (73.7)	3953 (75.4)	412 (75.3)			9160 (74.5)	9013 (74.5)	9386 (74.7)		
12 h-24 h	1681 (26.3)	1290 (24.6)	135 (24.7)			3137 (25.5)	3078 (25.5)	3184 (25.3)		
Body mass index, mean (SD)	23.9 (3.3)	23.9 (3.2)	24.1 (3.5)	0.053	0.058	24.0 (4.5)	23.9 (4.9)	23.8 (15.8)	0.012	0.010
NIHSS score, median (IQR)	2 (1 - 3)	2 (1 - 4)	2 (1 - 3)	0.137	0.026	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	0.005	0.006
TOAST				0.316	0.053				0.093	0.075
LAA	2332 (36.5)	2605 (49.7)	277 (50.6)			5313 (43.2)	5225 (43.2)	5397 (42.9)		
SVO	2311 (36.2)	1447 (27.6)	157 (28.7)			3872 (31.5)	3813 (31.5)	4308 (34.3)		
OE	204 (3.2)	176 (3.4)	16 (2.9)			406 (3.3)	411 (3.4)	293 (2.3)		
UD	1544 (24.2)	1015 (19.4)	97 (17.7)			2706 (22.0)	2642 (21.9)	2573 (20.5)		
History of TIA	94 (1.5)	168 (3.2)	32 (5.9)	0.235	0.128	307 (2.5)	289 (2.4)	298 (2.4)	0.008	0.001
History of stroke	639 (10.0)	1038 (19.8)	221 (40.4)	0.748	0.461	1943 (15.8)	1909 (15.8)	1723 (13.7)	0.059	0.059
History of PAD	14 (0.2)	27 (0.5)	6 (1.1)	0.109	0.065	58 (0.5)	46 (0.4)	39 (0.3)	0.026	0.012
History of CAD	250 (3.9)	490 (9.3)	78 (14.3)	0.366	0.153	862 (7.0)	819 (6.8)	712 (5.7)	0.055	0.046
Hypertension	3865 (60.5)	3603 (68.7)	410 (75.0)	0.313	0.139	8007 (65.1)	7837 (64.8)	8476 (67.4)	0.049	0.055
Diabetes mellitus	1870 (29.3)	1786 (34.1)	253 (46.3)	0.356	0.251	4006 (32.6)	3928 (32.5)	3860 (30.7)	0.040	0.038
Dyslipidemia	1761 (27.6)	1820 (34.7)	225 (41.1)	0.289	0.133	3770 (30.7)	3801 (31.4)	3659 (29.1)	0.034	0.051
Smoking status				0.218	0.156				0.051	0.069
Never smoker	3641 (57.0)	3093 (59.0)	339 (62.0)			7189 (58.5)	7028 (58.1)	7255 (57.7)		
Ex-smoker, >5 yrs.	504 (7.9)	480 (9.2)	53 (9.7)			1017 (8.3)	1029 (8.5)	956 (7.6)		
Recent smoker, within 5 yrs.	321 (5.0)	252 (4.8)	40 (7.3)			617 (5.0)	619 (5.1)	520 (4.1)		
Current smoker	1925 (30.1)	1418 (27.0)	115 (21.0)			3474 (28.3)	3415 (28.2)	3839 (30.5)		
Atrial fibrillation	41 (0.6)	25 (0.5)	6 (1.1)	0.049	0.070	89 (0.7)	67 (0.6)	63 (0.5)	0.029	0.007
Prior antiplatelet use	893 (14.0)	1742 (33.2)	320 (58.5)	1.045	0.524	3087 (25.1)	2975 (24.6)	2838 (22.6)	0.059	0.048
Prior antihypertensive use	2625 (41.1)	2727 (52.0)	346 (63.3)	0.455	0.229	5818 (47.3)	5699 (47.1)	5838 (46.4)	0.018	0.014
Prior statin use	759 (11.9)	1182 (22.5)	199 (36.4)	0.598	0.307	2165 (17.6)	2140 (17.7)	1962 (15.6)	0.054	0.056
Prior lipid-lowering agent use	101 (1.6)	120 (2.3)	17 (3.1)	0.101	0.051	255 (2.1)	242 (2.0)	172 (1.4)	0.055	0.049

Prior antidiabetic use	1314 (20.6)	1370 (26.1)	203 (37.1)	0.372	0.238	2961 (24.1)	2902 (24.0)	2777 (22.1)	0.047	0.045
Multiple lesions	515 (8.1)	667 (12.7)	67 (12.2)	0.139	0.014	1341 (10.9)	1283 (10.6)	1244 (9.9)	0.033	0.024
LASO				0.370	0.139				0.065	0.042
No stenosis	4155 (65.0)	2693 (51.4)	265 (48.4)			7064 (57.4)	6972 (57.7)	7270 (57.8)		
Mild (<50%)	525 (8.2)	581 (11.1)	76 (13.9)			1243 (10.1)	1210 (10.0)	1322 (10.5)		
Significant (≥50%)	992 (15.5)	1200 (22.9)	144 (26.3)			2376 (19.3)	2354 (19.5)	2379 (18.9)		
Occlusion	719 (11.3)	769 (14.7)	62 (11.3)			1614 (13.1)	1555 (12.9)	1600 (12.7)		
In-hospital treatment										
Anti-diabetics	1413 (22.1)	1360 (25.9)	198 (36.2)	0.314	0.223	3022 (24.6)	2968 (24.5)	3210 (25.5)	0.022	0.023
Anti-hypertensives	2624 (41.1)	2273 (43.4)	285 (52.1)	0.223	0.176	5246 (42.7)	5119 (42.3)	5645 (44.9)	0.045	0.052
Anti-lipid lowering agents	3713 (58.1)	3520 (67.1)	399 (72.9)	0.316	0.127	7735 (62.9)	7601 (62.9)	7928 (63.1)	0.003	0.004
Statins	5800 (90.8)	4885 (93.2)	498 (91.0)	0.010	0.079	11289 (91.8)	11121 (92.0)	11578 (92.1)	0.011	0.005
Lab finding, mean (SD)										
WBC count	8.0 (2.8)	8.0 (2.8)	8.0 (3.4)	0.007	0.006	8.0 (3.9)	8.0 (4.3)	7.9 (13.7)	0.015	0.014
Creatinine	0.93 (0.85)	1.03 (0.98)	1.12 (1.22)	0.176	0.073	1.02 (1.61)	1.00 (1.29)	0.99 (4.33)	0.010	0.003
Hemoglobin	13.9 (1.9)	13.8 (1.8)	13.4 (1.8)	0.285	0.199	13.8 (2.7)	13.8 (2.8)	13.8 (8.5)	0.001	0.002
Platelet count	233.8 (65.9)	236.3 (68.9)	230.4 (72.4)	0.049	0.084	235.3 (96.2)	235.0 (101.9)	233.1 (327.7)	0.009	0.008
LDL-cholesterol	114.8 (35.6)	108.5 (36.7)	100.2 (38.7)	0.394	0.221	111.2 (50.2)	111.5 (56.2)	113.0 (184.8)	0.013	0.011
Glucose	141.6 (60.3)	146.8 (64.7)	153.7 (67.7)	0.189	0.104	144.7 (87.6)	144.7 (94.3)	141.7 (287.7)	0.014	0.014
Systolic blood pressure	151.9 (28.5)	149.5 (26.9)	146.5 (26.9)	0.197	0.113	150.2 (38.5)	150.5 (41.5)	151.9 (137.9)	0.017	0.014

ASD: absolute standardized difference.

*An ASD of >0.1 is considered a meaningful imbalance.

Supplemental Table 5. Propensity score analysis of sensitivity analysis for NIHSS scores of 0-3

	Before multiple treatment PS					After multiple treatment PS				
	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	ASD1	ASD2	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	ASD1	ASD2
N	5112	3920	453			9570	9412	9639		
Age (yr), mean (SD)	63.7±13.4	66.1±12.5	67.8±11.4	0.329	0.143	65.0±17.9	65.0±19.8	66.4±55.9	0.035	0.034
Male, n (%)	3193 (62.5)	2473 (63.1)	262 (57.8)	0.095	0.108	5940 (62.1)	5868 (62.3)	6049 (62.8)	0.014	0.009
Onset-to-admission time				0.050	0.012				0.011	0.010
Within 12 h	3830 (74.9)	3040 (77.6)	349 (77.0)			7271 (76.0)	7156 (76.0)	7368 (76.4)		
12 h-24 h	1282 (25.1)	880 (22.4)	104 (23.0)			2299 (24.0)	2256 (24.0)	2270 (23.6)		
Body mass index, mean (SD)	24.0±3.3	24.0±3.2	24.1±3.4	0.038	0.024	24.0±4.4	24.0±5.0	24.0±15.5	0.006	0.005
NIHSS score, median (IQR)	1 (0 - 2)	1 (0 - 2)	2 (1 - 3)	0.108	0.093	1 (0 - 2)	1 (0 - 2)	1 (1 - 3)	0.021	0.023
TOAST				0.298	0.081				0.118	0.118
LAA	1808 (35.4)	1893 (48.3)	222 (49.0)			3973 (41.5)	3920 (41.6)	4131 (42.9)		
SVO	1816 (35.5)	1082 (27.6)	135 (29.8)			3013 (31.5)	2962 (31.5)	3052 (31.7)		
OE	174 (3.4)	150 (3.8)	13 (2.9)			339 (3.5)	349 (3.7)	241 (2.5)		
UD	1314 (25.7)	795 (20.3)	83 (18.3)			2245 (23.5)	2182 (23.2)	2214 (23.0)		
History of TIA	73 (1.4)	143 (3.6)	22 (4.9)	0.197	0.060	254 (2.7)	233 (2.5)	240 (2.5)	0.010	0.001
History of stroke	474 (9.3)	750 (19.1)	180 (39.7)	0.757	0.464	1441 (15.1)	1406 (14.9)	1295 (13.4)	0.046	0.043
History of PAD	10 (0.2)	19 (0.5)	2 (0.4)	0.044	0.006	39 (0.4)	30 (0.3)	18 (0.2)	0.040	0.027
History of CAD	206 (4.0)	376 (9.6)	71 (15.7)	0.398	0.184	690 (7.2)	653 (6.9)	530 (5.5)	0.070	0.060
Hypertension	3024 (59.2)	2641 (67.4)	336 (74.2)	0.323	0.150	6088 (63.6)	5965 (63.4)	6458 (67.0)	0.071	0.076
Diabetes mellitus	1420 (27.8)	1282 (32.7)	194 (42.8)	0.319	0.210	2958 (30.9)	2916 (31.0)	2930 (30.4)	0.011	0.013
Dyslipidemia	1375 (26.9)	1375 (35.1)	171 (37.7)	0.234	0.056	2889 (30.2)	2907 (30.9)	2696 (28.0)	0.049	0.064
Smoking status				0.219	0.122				0.023	0.052
Never smoker	2899 (56.7)	2313 (59.0)	279 (61.6)			5571 (58.2)	5452 (57.9)	5482 (56.9)		
Ex-smoker, >5yr	415 (8.1)	374 (9.5)	48 (10.6)			812 (8.5)	826 (8.8)	768 (8.0)		
Recent smoker, within 5yr	265 (5.2)	201 (5.1)	28 (6.2)			502 (5.2)	494 (5.2)	445 (4.6)		
Current smoker	1533 (30.0)	1032 (26.3)	98 (21.6)			2685 (28.1)	2640 (28.1)	2944 (30.5)		
Atrial fibrillation	34 (0.7)	20 (0.5)	8 (1.8)	0.101	0.119	76 (0.8)	58 (0.6)	49 (0.5)	0.036	0.015
Prior antiplatelet use	702 (13.7)	1322 (33.7)	253 (55.8)	0.986	0.456	2373 (24.8)	2283 (24.3)	2234 (23.2)	0.038	0.025
Prior antihypertensive use	2071 (40.5)	2008 (51.2)	278 (61.4)	0.427	0.206	4441 (46.4)	4347 (46.2)	4673 (48.5)	0.042	0.046
Prior statin use	613 (12.0)	919 (23.4)	155 (34.2)	0.547	0.240	1704 (17.8)	1687 (17.9)	1530 (15.9)	0.052	0.055
Prior lipid-lowering agent use	75 (1.5)	92 (2.3)	13 (2.9)	0.096	0.033	186 (1.9)	179 (1.9)	140 (1.4)	0.039	0.035

Prior antidiabetic use	1006 (19.7)	994 (25.4)	154 (34.0)	0.327	0.190	2202 (23.0)	2174 (23.1)	2112 (21.9)	0.026	0.028
Multiple lesions	420 (8.2)	506 (12.9)	57 (12.6)	0.143	0.010	1067 (11.2)	1018 (10.8)	993 (10.3)	0.027	0.017
LASO				0.360	0.120				0.050	0.035
No stenosis	3352 (65.6)	2043 (52.1)	223 (49.2)			5581 (58.3)	5501 (58.4)	5470 (56.7)		
Mild (<50%)	411 (8.0)	388 (9.9)	60 (13.2)			900 (9.4)	889 (9.5)	939 (9.7)		
Significant (≥50%)	795 (15.6)	923 (23.5)	116 (25.6)			1854 (19.4)	1845 (19.6)	1974 (20.5)		
Occlusion	554 (10.8)	566 (14.4)	54 (11.9)			1236 (12.9)	1176 (12.5)	1257 (13.0)		
In-hospital treatment										
Anti-diabetics	1070 (20.9)	987 (25.2)	150 (33.1)	0.277	0.175	2235 (23.4)	2200 (23.4)	2400 (24.9)	0.036	0.036
Anti-hypertensives	2062 (40.3)	1635 (41.7)	240 (53.0)	0.256	0.227	3990 (41.7)	3877 (41.2)	4260 (44.2)	0.051	0.061
Anti-lipid lowering agents	2968 (58.1)	2591 (66.1)	327 (72.2)	0.300	0.132	5965 (62.3)	5877 (62.4)	5960 (61.8)	0.010	0.012
Statins	4628 (90.5)	3651 (93.1)	405 (89.4)	0.038	0.133	8767 (91.6)	8649 (91.9)	8820 (91.5)	0.004	0.014
Lab finding, mean (SD)										
WBC count	8.0±2.9	8.0±2.8	8.1±3.5	0.006	0.011	8.0±4.0	8.0±4.3	8.0±13.2	0.009	0.008
Creatinine	0.93±0.85	1.02±0.94	1.07±0.95	0.160	0.052	1.00±1.50	0.99±1.26	0.99±3.94	0.001	0.003
Hemoglobin	14.0±1.9	13.8±1.8	13.5±1.8	0.273	0.197	13.9±2.6	13.9±2.8	13.9±7.9	0.000	0.001
Platelet count	233.4±65.0	235.9±69.0	230.2±70.0	0.047	0.082	235.5±94.9	234.7±104.0	236.3±314.0	0.004	0.007
LDL-cholesterol	114.0±35.0	107.7±36.0	100.3±36.8	0.383	0.204	110.4±48.7	110.7±55.8	111.5±167.4	0.008	0.006
Glucose	139.8±58.4	145.3±63.0	149.9±66.3	0.162	0.071	142.7±83.6	142.9±92.9	141.4±279.1	0.006	0.007
Systolic blood pressure	150.9±28.0	149.1±26.8	145.5±26.0	0.203	0.137	149.5±37.5	149.7±41.9	151.8±128.0	0.024	0.021

Supplemental Table 6. Sensitivity analysis for NIHSS scores of 0-3

	crude HR (95% CI)	p	adjusted HR (95% CI)	p	IPTW ^b , weighted HR (95% CI)	P
Primary outcome						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	0.98 (0.76-1.27)	0.8862	1.25 (0.95-1.64)	0.1100	0.96 (0.65-1.40)	0.8199
clopidogrel-aspirin	0.83 (0.63-1.08)	0.1699	0.91 (0.69-1.19)	0.4734	0.69 (0.47-1.02)	0.0623
All-stroke						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	0.94 (0.72-1.23)	0.6461	1.18 (0.89-1.55)	0.2525	0.89 (0.61-1.31)	0.5627
clopidogrel-aspirin	0.80 (0.61-1.05)	0.1022	0.86 (0.65-1.13)	0.2695	0.65 (0.44-0.96)	0.0296
All-cause mortality						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	1.98 (0.62-6.29)	0.2467	2.97 (0.91-9.67)	0.0700	8.08 (2.11-30.98)	0.0023
clopidogrel-aspirin	1.70 (0.53-5.47)	0.3722	2.19 (0.67-7.16)	0.1948	6.03 (1.56-23.34)	0.0092
MI ^a						
other combination	1(Ref)					
aspirin monotherapy	1.47 (0.08-28.17)	0.7977	Non-estimable		Non-estimable	
clopidogrel-aspirin	3.02 (0.16-56.05)	0.4586	Non-estimable		Non-estimable	

Adjusted variables: age; male sex; initial NIHSS score; arrival time; TOAST classification; history of TIA, stroke, CAD, PAD; HTN; DM; dyslipidemia; smoking; atrial fibrillation; prior antiplatelet, antihypertensive, antidiabetic, statin, or lipid-lowering agent use; multiple lesions; LASO; discharge medications of antihypertensives, antidiabetics, statins, and lipid-lowering agents; creatinine; hemoglobin; platelet count; LDL-C; glucose; and SBP.

^a Cox PH regression using Firth's penalized maximum likelihood method.

^b Weighted Cox proportional hazards model with robust standard errors.

Supplemental Table 7. Propensity score analysis of sensitivity analysis for patients with first ever stroke

	Before multiple treatment PS					After multiple treatment PS				
	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	ASD1	ASD2	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	ASD1	ASD2
N	5752	4205	347			10388	10229	10386		
Age (yrs.), mean (SD)	63.9±13.5	66.1±12.7	67.9±11.8	0.316	0.146	65.0±17.8	65.0±20.1	65.5±69.2	0.010	0.008
Male, n (%)	3530 (61.4)	2610 (62.1)	193 (55.6)	0.117	0.131	6369 (61.3)	6273 (61.3)	6442 (62.0)	0.015	0.015
Onset-to-admission time				0.031	0.069				0.007	0.007
Within 12 h	4223 (73.4)	3157 (75.1)	250 (72.0)			7689 (74.0)	7569 (74.0)	7718 (74.3)		
12 h-24 h	1529 (26.6)	1048 (24.9)	97 (28.0)			2699 (26.0)	2660 (26.0)	2668 (25.7)		
Body mass index, mean (SD)	23.9±3.3	23.9±3.3	24.1±3.3	0.044	0.051	23.9±4.4	23.9±5.1	23.9±17.4	0.006	0.005
NIHSS score, median (IQR)	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	0.094	0.011	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	0.014	0.014
TOAST				0.275	0.069				0.080	0.080
LAA	2056 (35.7)	2053 (48.8)	171 (49.3)			4362 (42.0)	4293 (42.0)	4195 (40.4)		
SVO	2132 (37.1)	1199 (28.5)	106 (30.5)			3401 (32.7)	3348 (32.7)	3687 (35.5)		
OE	189 (3.3)	152 (3.6)	9 (2.6)			366 (3.5)	366 (3.6)	264 (2.5)		
UD	1375 (23.9)	801 (19.0)	61 (17.6)			2260 (21.8)	2222 (21.7)	2239 (21.6)		
History of TIA	77 (1.3)	134 (3.2)	20 (5.8)	0.241	0.125	229 (2.2)	227 (2.2)	218 (2.1)	0.007	0.008
History of PAD	11 (0.2)	21 (0.5)	3 (0.9)	0.093	0.044	30 (0.3)	34 (0.3)	25 (0.2)	0.009	0.016
History of CAD	188 (3.3)	364 (8.7)	39 (11.2)	0.311	0.086	597 (5.7)	591 (5.8)	497 (4.8)	0.043	0.044
Hypertension	3364 (58.5)	2773 (65.9)	244 (70.3)	0.249	0.094	6444 (62.0)	6338 (62.0)	6811 (65.6)	0.074	0.075
Diabetes mellitus	1611 (28.0)	1345 (32.0)	135 (38.9)	0.233	0.145	3157 (30.4)	3107 (30.4)	3142 (30.3)	0.003	0.003
Dyslipidemia	1543 (26.8)	1334 (31.7)	115 (33.1)	0.138	0.030	3005 (28.9)	3003 (29.4)	3041 (29.3)	0.008	0.002
Smoking status				0.129	0.069				0.061	0.061
Never smoker	3244 (56.4)	2423 (57.6)	213 (61.4)			5944 (57.2)	5850 (57.2)	5834 (56.2)		
Ex-smoker, >5 yrs.	451 (7.8)	368 (8.8)	31 (8.9)			840 (8.1)	841 (8.2)	795 (7.7)		
Recent smoker, within 5 yrs.	283 (4.9)	189 (4.5)	15 (4.3)			496 (4.8)	490 (4.8)	416 (4.0)		
Current smoker	1774 (30.8)	1225 (29.1)	88 (25.4)			3108 (29.9)	3047 (29.8)	3341 (32.2)		
Atrial fibrillation	37 (0.6)	18 (0.4)	5 (1.4)	0.079	0.105	59 (0.6)	57 (0.6)	39 (0.4)	0.027	0.026
Prior antiplatelet use	544 (9.5)	942 (22.4)	125 (36.0)	0.668	0.303	1701 (16.4)	1632 (16.0)	1552 (14.9)	0.039	0.028
Prior antihypertensive use	2222 (38.6)	2005 (47.7)	193 (55.6)	0.345	0.159	4487 (43.2)	4417 (43.2)	4538 (43.7)	0.010	0.010
Prior statin use	563 (9.8)	691 (16.4)	67 (19.3)	0.273	0.075	1362 (13.1)	1324 (12.9)	1294 (12.5)	0.020	0.015
Prior lipid-lowering agent use	90 (1.6)	85 (2.0)	5 (1.4)	0.010	0.045	205 (2.0)	184 (1.8)	196 (1.9)	0.007	0.006
Prior antidiabetic use	1108 (19.3)	1005 (23.9)	101 (29.1)	0.231	0.118	2252 (21.7)	2228 (21.8)	2201 (21.2)	0.012	0.014

Multiple lesions	450 (7.8)	533 (12.7)	44 (12.7)	0.161	0.000	1080 (10.4)	1054 (10.3)	1007 (9.7)	0.023	0.020
LASO				0.320	0.142				0.031	0.031
No stenosis	3789 (65.9)	2199 (52.3)	181 (52.2)			6126 (59.0)	6047 (59.1)	6062 (58.4)		
Mild (<50%)	451 (7.8)	454 (10.8)	48 (13.8)			1011 (9.7)	980 (9.6)	1022 (9.8)		
Significant (≥50%)	884 (15.4)	939 (22.3)	79 (22.8)			1928 (18.6)	1923 (18.8)	1973 (19.0)		
Occlusion	628 (10.9)	613 (14.6)	39 (11.2)			1322 (12.7)	1278 (12.5)	1329 (12.8)		
In-hospital treatment										
Anti-diabetics	1230 (21.4)	1057 (25.1)	108 (31.1)	0.223	0.133	2434 (23.4)	2394 (23.4)	2738 (26.4)	0.068	0.068
Anti-hypertensives	2326 (40.4)	1796 (42.7)	172 (49.6)	0.184	0.138	4313 (41.5)	4232 (41.4)	4552 (43.8)	0.047	0.050
Anti-lipid lowering agents	3355 (58.3)	2827 (67.2)	247 (71.2)	0.272	0.086	6525 (62.8)	6409 (62.7)	6432 (61.9)	0.018	0.015
Statins	5225 (90.8)	3924 (93.3)	311 (89.6)	0.041	0.132	9540 (91.8)	9414 (92.0)	9446 (90.9)	0.032	0.039
Lab finding, mean (SD)										
WBC count	8.1±2.8	8.1±2.8	8.1±3.5	0.015	0.011	8.1±3.8	8.1±4.4	7.9±15.5	0.013	0.012
Creatinine	0.91±0.80	1.01±0.94	1.10±1.29	0.175	0.073	0.98±1.54	0.97±1.23	0.96±4.67	0.008	0.003
Hemoglobin	14.0±1.9	13.9±1.8	13.6±1.8	0.211	0.139	13.9±2.6	13.9±2.8	13.9±9.7	0.001	0.001
Platelet count	234.6±65.9	237.7±68.0	232.0±69.3	0.038	0.084	236.7±93.3	236.2±103.2	236.5±377.5	0.001	0.001
LDL-cholesterol	116.3±35.3	111.9±35.9	109.7±39.2	0.176	0.060	114.1±47.9	114.4±56.5	114.7±206.5	0.004	0.002
Glucose	141.1±60.0	147.1±65.5	148.8±66.0	0.122	0.026	144.1±85.5	144.1±96.2	143.1±343.0	0.004	0.004
Systolic blood pressure	152.5±28.5	149.7±27.4	146.6±26.4	0.216	0.116	151.0±37.7	151.1±43.4	152.6±154.5	0.014	0.013

Supplemental Table 8. Sensitivity analysis for patients with first-ever stroke

	crude HR (95% CI)	p	adjusted HR (95% CI)	p	IPTW ^b , weighted HR (95% CI)	P
Composite events of stroke, MI, and all-death						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	0.91 (0.69-1.21)	0.5301	1.05 (0.79-1.40)	0.7118	0.96 (0.67-1.38)	0.8315
clopidogrel-aspirin	0.86 (0.65-1.14)	0.3004	0.88 (0.66-1.17)	0.3813	0.82 (0.57-1.18)	0.2738
all-stroke						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	0.87 (0.66-1.15)	0.3369	1.00 (0.75-1.33)	0.9960	0.90 (0.63-1.30)	0.5855
clopidogrel-aspirin	0.82 (0.62-1.09)	0.1799	0.84 (0.63-1.12)	0.2289	0.77 (0.53-1.11)	0.1628
all-death						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	4.49 (0.62-32.28)	0.1356	6.58 (0.90-47.79)	0.0627	13.84 (1.91-100.17)	0.0093
clopidogrel-aspirin	4.22 (0.58-30.51)	0.1537	5.24 (0.72-38.23)	0.1021	11.13 (1.53-81.04)	0.0174
MI ^a						
other combination	1(Ref)					
aspirin monotherapy	1.22 (0.06-23.07)	0.8927	Non-estimable		Non-estimable	
clopidogrel-aspirin	1.83 (0.10-34.29)	0.6862	Non-estimable		Non-estimable	

Adjusted variables: age; male sex; initial NIHSS score; arrival time; TOAST classification; history of TIA, stroke, CAD, PAD; HTN; DM; dyslipidemia; smoking; atrial fibrillation; prior antiplatelet, antihypertensive, antidiabetic, statin, or lipid-lowering agent use; multiple lesions; LASO; discharge medications of antihypertensives, antidiabetics, statins, and lipid-lowering agents; creatinine; hemoglobin; platelet count; LDL-C; glucose; and SBP.

^a Cox PH regression using Firth's penalized maximum likelihood method.

^b Weighted Cox proportional hazards model with robust standard errors.

Supplemental Table 9. Propensity score analysis of sensitivity analysis for the study periods between 2014 and 2018

	Before multiple treatment PS					After multiple treatment PS				
	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	AM vs other ASD1	C-A vs other ASD2	Aspirin monotherapy	Clopidogrel-aspirin	Other combination	AM vs other ASD1	C-A vs other ASD2
N	3815	4077	394			8347	8253	8403		
Age (yrs.), mean (SD)	64.7±13.6	66.7±12.6	68.2±11.9	0.276	0.119	66.0±19.5	65.9±18.2	66.1±58.6	0.003	0.003
Male, n (%)	2350 (61.6)	2565 (62.9)	230 (58.4)	0.066	0.093	5170 (61.9)	5117 (62.0)	5016 (59.7)	0.046	0.047
Onset-to-admission time				0.105	0.060				0.018	0.021
Within 12 h	2801 (73.4)	3073 (75.4)	307 (77.9)			6214 (74.5)	6153 (74.6)	6189 (73.7)		
12 h-24 h	1014 (26.6)	1004 (24.6)	87 (22.1)			2133 (25.5)	2100 (25.4)	2214 (26.3)		
Body mass index, mean (SD)	24.0±3.4	24.0±3.2	24.1±3.4	0.038	0.045	24.0±5.0	24.0±4.6	23.9±15.0	0.011	0.010
NIHSS score, median (IQR)	2 (1 - 3)	2 (1 - 3)	2 (1 - 4)	0.139	0.036	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	0.020	0.024
TOAST				0.330	0.065				0.113	0.114
LAA	1314 (34.4)	1955 (48.0)	198 (50.3)			3552 (42.6)	3478 (42.1)	3365 (40.0)		
SVO	1397 (36.6)	1177 (28.9)	115 (29.2)			2630 (31.5)	2631 (31.9)	3070 (36.5)		
OE	144 (3.8)	143 (3.5)	12 (3.0)			305 (3.7)	306 (3.7)	277 (3.3)		
UD	960 (25.2)	802 (19.7)	69 (17.5)			1860 (22.3)	1839 (22.3)	1691 (20.1)		
History of TIA	47 (1.2)	125 (3.1)	14 (3.6)	0.152	0.027	175 (2.1)	183 (2.2)	198 (2.4)	0.017	0.009
History of stroke	388 (10.2)	774 (19.0)	168 (42.6)	0.792	0.530	1338 (16.0)	1339 (16.2)	1213 (14.4)	0.045	0.050
History of PAD	6 (0.2)	22 (0.5)	2 (0.5)	0.061	0.004	26 (0.3)	30 (0.4)	18 (0.2)	0.020	0.028
History of CAD	170 (4.5)	352 (8.6)	57 (14.5)	0.347	0.183	615 (7.4)	580 (7.0)	539 (6.4)	0.038	0.025
Hypertension	2304 (60.4)	2733 (67.0)	290 (73.6)	0.284	0.144	5408 (64.8)	5325 (64.5)	5747 (68.4)	0.076	0.082
Diabetes mellitus	1088 (28.5)	1355 (33.2)	176 (44.7)	0.340	0.236	2658 (31.9)	2626 (31.8)	2650 (31.5)	0.007	0.006
Dyslipidemia	984 (25.8)	1359 (33.3)	154 (39.1)	0.287	0.120	2461 (29.5)	2489 (30.2)	2477 (29.5)	0.000	0.015
Smoking status				0.197	0.121				0.049	0.063
Never smoker	2192 (57.5)	2430 (59.6)	242 (61.4)			4936 (59.1)	4853 (58.8)	5013 (59.7)		
Ex-smoker, >5 yrs.	311 (8.2)	363 (8.9)	38 (9.6)			694 (8.3)	704 (8.5)	641 (7.6)		
Recent smoker, within 5 yrs.	193 (5.1)	202 (5.0)	26 (6.6)			426 (5.1)	430 (5.2)	318 (3.8)		
Current smoker	1119 (29.3)	1082 (26.5)	88 (22.3)			2290 (27.4)	2266 (27.5)	2430 (28.9)		
Atrial fibrillation	26 (0.7)	17 (0.4)	5 (1.3)	0.060	0.093	47 (0.6)	47 (0.6)	34 (0.4)	0.022	0.022
Prior antiplatelet use	545 (14.3)	1255 (30.8)	222 (56.3)	0.980	0.534	2094 (25.1)	2032 (24.6)	1925 (22.9)	0.051	0.040

Prior antihypertensive use	1572 (41.2)	2054 (50.4)	235 (59.6)	0.375	0.187	3928 (47.1)	3864 (46.8)	3977 (47.3)	0.005	0.010
Prior statin use	532 (13.9)	909 (22.3)	140 (35.5)	0.517	0.295	1574 (18.9)	1576 (19.1)	1510 (18.0)	0.023	0.029
Prior lipid-lowering agent use	99 (2.6)	119 (2.9)	18 (4.6)	0.106	0.087	238 (2.9)	235 (2.8)	201 (2.4)	0.029	0.028
Prior antidiabetic use	755 (19.8)	1014 (24.9)	139 (35.3)	0.352	0.228	1925 (23.1)	1914 (23.2)	1917 (22.8)	0.006	0.009
Multiple lesions	325 (8.5)	548 (13.4)	53 (13.5)	0.158	0.000	983 (11.8)	934 (11.3)	885 (10.5)	0.040	0.025
LASO				0.377	0.189				0.027	0.050
No stenosis	2498 (65.5)	2171 (53.2)	195 (49.5)			4813 (57.7)	4802 (58.2)	4967 (59.1)		
Mild (<50%)	295 (7.7)	418 (10.3)	54 (13.7)			814 (9.8)	782 (9.5)	876 (10.4)		
Significant (≥50%)	583 (15.3)	893 (21.9)	102 (25.9)			1584 (19.0)	1587 (19.2)	1488 (17.7)		
Occlusion	439 (11.5)	595 (14.6)	43 (10.9)			1135 (13.6)	1083 (13.1)	1073 (12.8)		
In-hospital treatment										
Anti-diabetics	796 (20.9)	1015 (24.9)	140 (35.5)	0.330	0.233	1967 (23.6)	1951 (23.6)	2227 (26.5)	0.068	0.066
Anti-hypertensives	1510 (39.6)	1648 (40.4)	195 (49.5)	0.200	0.183	3388 (40.6)	3350 (40.6)	3593 (42.8)	0.044	0.044
Anti-lipid lowering agents	2204 (57.8)	2660 (65.2)	291 (73.9)	0.344	0.188	5208 (62.4)	5144 (62.3)	5262 (62.6)	0.005	0.006
Statins	3576 (93.7)	3799 (93.2)	361 (91.6)	0.081	0.059	7770 (93.1)	7704 (93.3)	7737 (92.1)	0.039	0.049
Lab finding, mean (SD)										
WBC count	8.1±2.8	8.0±2.8	7.9±3.2	0.068	0.044	8.1±4.2	8.1±4.0	8.1±4.8	0.003	0.004
Creatinine	0.93±0.85	1.02±0.89	1.09±1.15	0.153	0.072	1.00±1.58	0.99±1.15	0.99±4.25	0.004	0.001
Hemoglobin	13.9±1.9	13.8±1.8	13.4±1.8	0.273	0.202	13.8±2.9	13.8±2.6	13.9±8.4	0.004	0.003
Platelet count	235.3±66.1	236.4±68.3	228.8±72.8	0.093	0.107	235.7±100.8	235.6±95.4	234.5±320.4	0.005	0.005
LDL-cholesterol	113.8±35.4	108.6±37.1	99.7±38.9	0.379	0.236	110.5±52.9	110.5±52.6	113.2±181.8	0.020	0.020
Glucose	142.8±60.3	146.9±63.8	152.3±65.1	0.151	0.083	145.4±92.0	145.3±88.4	144.5±278.2	0.005	0.004
Systolic blood pressure	152.4±28.9	150.1±27.4	146.5±26.0	0.216	0.135	150.7±41.7	151.0±39.4	151.8±126.2	0.012	0.008

Supplemental Table 10. Sensitivity analysis for patients between 2014 and 2018

	crude HR (95% CI)	p	adjusted HR (95% CI)	p	IPTW ^b , weighted HR (95% CI)	P
Primary outcome						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	0.83 (0.64-1.07)	0.1516	0.96 (0.74-1.26)	0.7910	0.85 (0.59-1.24)	0.4099
clopidogrel-aspirin	0.80 (0.62-1.04)	0.0962	0.82 (0.63-1.06)	0.1357	0.72 (0.49-1.04)	0.0783
All-stroke						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	0.79 (0.61-1.02)	0.0727	0.91 (0.69-1.20)	0.5015	0.79 (0.54-1.15)	0.2238
clopidogrel-aspirin	0.78 (0.60-1.01)	0.0627	0.79 (0.60-1.03)	0.0836	0.68 (0.47-0.99)	0.0425
All-cause mortality						
other combination	1(Ref)		1(Ref)		1(Ref)	
aspirin monotherapy	1.76 (0.55-5.62)	0.3421	1.83 (0.56-5.98)	0.3207	7.86 (2.01-30.79)	0.0031
clopidogrel-aspirin	1.50 (0.47-4.82)	0.4943	1.23 (0.38-4.04)	0.7280	5.41 (1.38-21.18)	0.0153
MI ^a						
other combination	1(Ref)					
aspirin monotherapy	1.50 (0.08-29.37)	0.7887	Non-estimable		Non-estimable	
clopidogrel-aspirin	2.35 (0.12-44.30)	0.5680	Non-estimable		Non-estimable	

adjusted variables: age; male sex; initial NIHSS score; arrival time; TOAST classification; history of TIA, stroke, CAD, PAD; HTN; DM; dyslipidemia; smoking; atrial fibrillation; prior antiplatelet, antihypertensive, antidiabetic, statin, or lipid-lowering agent use; multiple lesions; LASO; discharge medications of antihypertensives, antidiabetics, statins, and lipid-lowering agents; creatinine; hemoglobin; platelet count; LDL-C; glucose; and SBP.

^a Cox PH regression using Firth's penalized maximum likelihood method.

^b Weighted Cox proportional hazards model with robust standard errors.