

Supplementary Online Content

Shoamanesh A, Hart RG, Connolly SJ, et al. Microbleeds and the effect of anticoagulation in patients with embolic stroke of undetermined source: an exploratory analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol*. Published online October 19, 2020. doi:10.1001/jamaneurol.2020.3836

eFigure. Kaplan-Meier Curves for Outcomes Stratified by CMB Burden

eTable 1. Baseline Characteristics and MRI Findings Between Included and Excluded Cohorts

eTable 2. Baseline Characteristics and MRI According to Number of Cerebral Microbleed Burden

eTable 3. Baseline Characteristics and MRI Findings by Cerebral Microbleed Topography

eTable 4. Recurrent Stroke Subtypes by Cerebral Microbleed Status

eTable 5. Efficacy in CMB Subgroups -- Recurrent Stroke

eTable 6. Efficacy in CMB Subgroups -- Ischemic Stroke

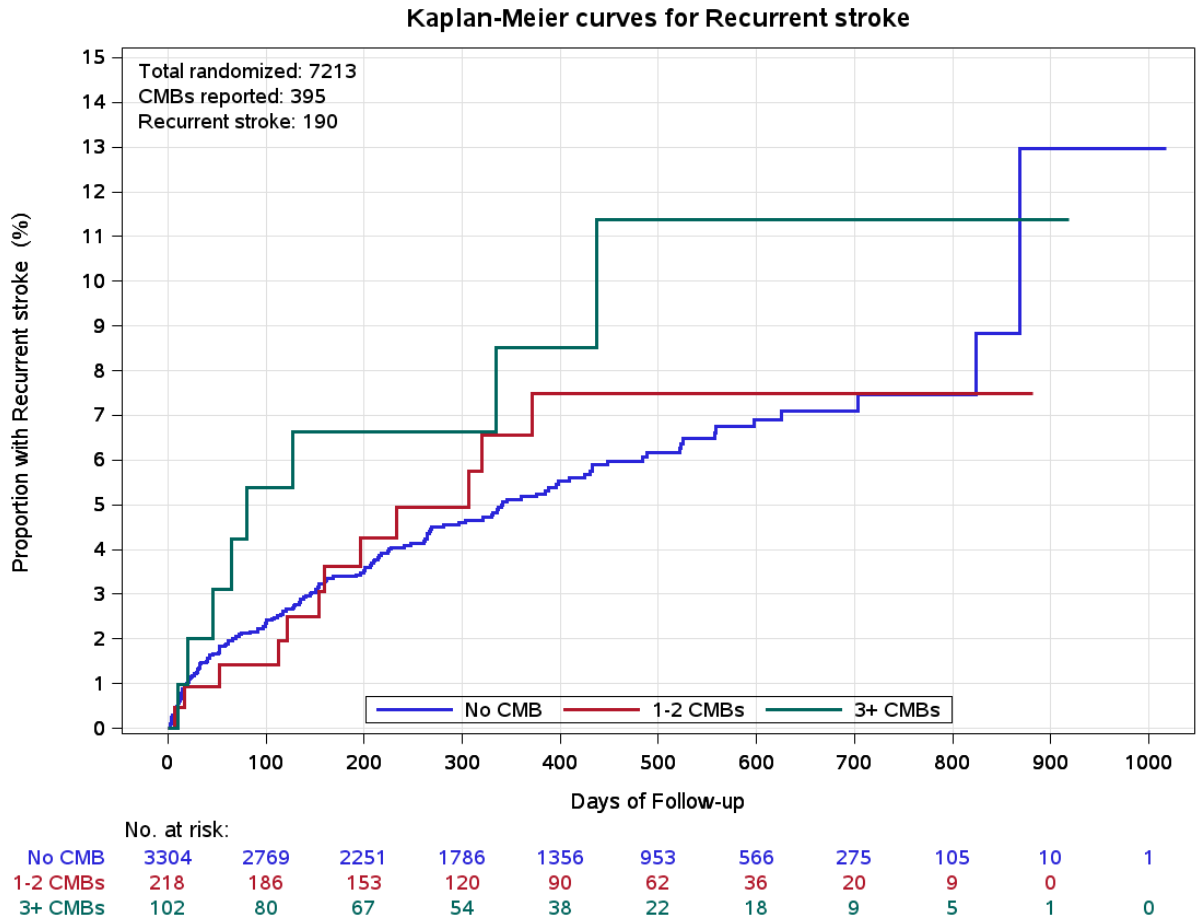
eTable 7. Efficacy in CMB Subgroups --All-Cause Mortality

eTable 8. Efficacy in CMB Subgroups --Intracerebral Hemorrhage

This supplementary material has been provided by the authors to give readers additional information about their work.

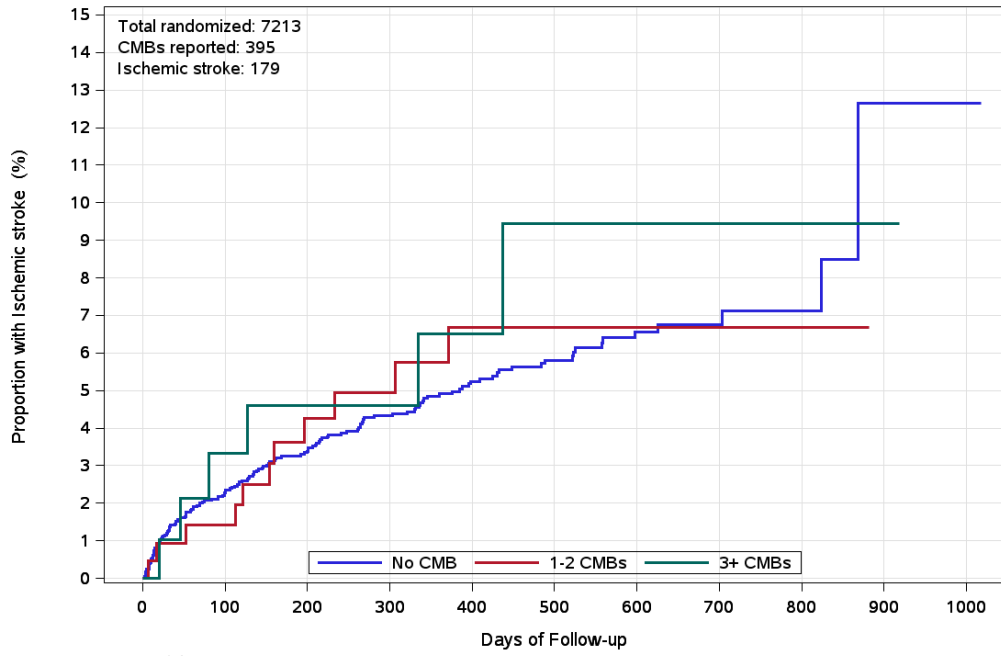
eFigure. Kaplan-Meier Curves for Outcomes Stratified by CMB Burden

a) Recurrent stroke



b) Ischemic stroke

Kaplan-Meier curves for Ischemic stroke

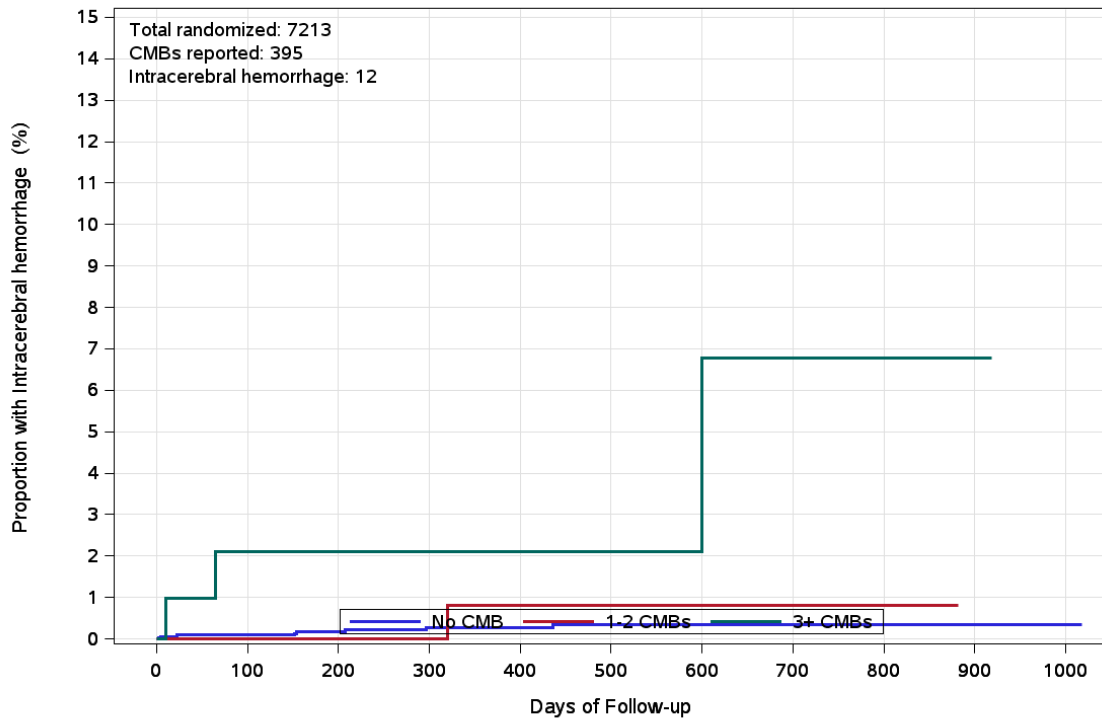


No. at risk:

	0	100	200	300	400	500	600	700	800	900	1000
No CMB	3304	2769	2251	1786	1356	953	566	275	105	10	1
1-2 CMBs	218	186	153	120	90	62	36	20	9	0	0
3+ CMBs	102	80	67	54	38	22	18	9	5	1	0

c) Intracerebral Hemorrhage

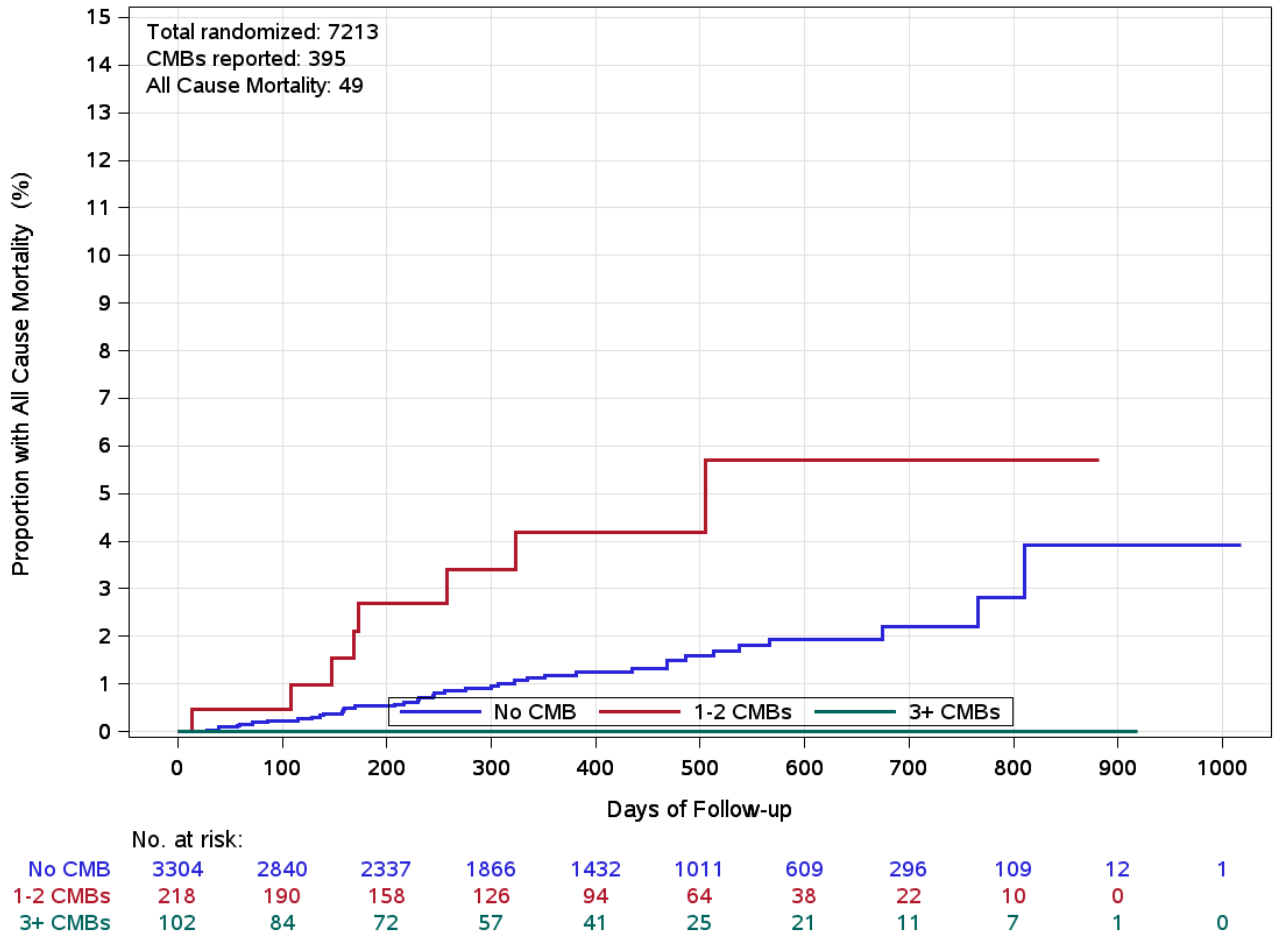
Kaplan-Meier curves for Intracerebral hemorrhage



No. at risk:		0	100	200	300	400	500	600	700	800	900	1000
No CMB	3304	2837	2332	1860	1428	1008	608	295	108	11	1	
1-2 CMBs	218	190	158	126	94	64	38	22	10	0		
3+ CMBs	102	82	70	55	40	25	21	11	7	1	0	

d) All-Cause Mortality

Kaplan-Meier curves for All Cause Mortality



eTable 1. Baseline Characteristics and MRI Findings Between Included and Excluded Cohorts

Characteristic	Included cohort _{USEP} (N=3699)	Excluded cohort _{USEP} (N=3514)	pvalue
Age, years (mean ± s.d.)	67.0±9.8	66.8±9.7	0.3776
Age<60 years	23 %	24 %	0.4064
Male sex	63 %	60 %	0.0466
Race:			
White only	65 %	80 %	<.0001
Black only	2 %	1 %	0.6911
East Asian only	25 %	14 %	<.0001
Others (includes not reported/multiracial)	8 %	5 %	<.0001

Global region:			
U.S.A. and Canada	16 %	9 %	<.0001
Latin America	7 %	14 %	<.0001
Western Europe	45 %	41 %	0.0009
Eastern Europe	8 %	23 %	<.0001
East Asia	24 %	14 %	<.0001
Medical history:			
Hypertension	76 %	79 %	0.0002
Diabetes mellitus	25 %	25 %	0.6184
Current tobacco use	21 %	20 %	0.8266
Coronary artery disease	6 %	7 %	0.1262
Heart failure	2 %	5 %	<.0001
Cancer	10 %	7 %	<.0001
Bioprosthetic heart valve	0 %	0 %	0.4392
TIA	19 %	16 %	0.0008
Renal dysfunction	3 %	3 %	0.1203
Liver disease	2 %	1 %	0.3380
History of GI bleeding	2 %	1 %	0.0167
CHADS ₂ (median, IQR)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	0.0026
CHA ₂ DS ₂ -VASc (median, IQR)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	0.0728
Estimated glomerular filtration rate (eGFR), mL/min per 1.73 m ²	77.9±20.3	79.4±20.8	0.0011
Functional measures at randomization:			
EQ-5D (median, IQR)	80.0 (65.0, 90.0)	75.0 (60.0, 85.0)	<.0001
MoCA (median, IQR)	25.0 (21.0, 27.0)	24.0 (20.0, 27.0)	<.0001
NIHSS score at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	<.0001
Modified Rankin Scale (mRS) at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	<.0001

eTable 2. Baseline Characteristics and MRI According to Number of Cerebral Microbleed Burden

Characteristic	Mild (1-2 CMBs) (N=218)	Moderate (3-10 CMBs) (N=85)	Severe (>10 CMBs) (N=17)	pvalue
Age, years (mean ± s.d.)	70.1±9.6	68.7±9.4	69.4±7.4	0.55
Age<60 years	16 %	20 %	6 %	0.32
Male sex	58 %	65 %	71 %	0.37
Race:				
White only	54 %	26 %	29 %	<0.0001
Black only	3 %	2 %	6 %	0.72
East Asian only	36 %	62 %	59 %	<0.0001
Others (includes not reported/multiracial)	8 %	9 %	6 %	0.85
Global region:				
U.S.A. and Canada	18 %	13 %	12 %	0.51
Latin America	2 %	4 %	6 %	0.46
Western Europe	40 %	20 %	24 %	0.00
Eastern Europe	6 %	2 %	0 %	0.26
East Asia	34 %	61 %	59 %	<0.0001
Medical history:				
Hypertension	83 %	91 %	100 %	0.05
Diabetes mellitus	27 %	24 %	29 %	0.78
Current tobacco use	20 %	22 %	18 %	0.87
Coronary artery disease	9 %	4 %	0 %	0.14
Heart failure	3 %	0 %	0 %	0.19
Cancer	11 %	5 %	6 %	0.21
Prior stroke or TIA	19 %	27 %	41 %	0.06
Renal dysfunction	5 %	4 %	0 %	0.63
Liver disease	2 %	2 %	0 %	0.82
History of GI bleeding	3 %	2 %	6 %	0.72
CHADS2 (median, IQR)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	4.0(3.0, 4.0)	0.61
CHA ₂ DS ₂ -VASc (median, IQR)	5.0 (4.0, 5.0)	5.0 (4.0, 5.0)	5.0(4.0, 5.0)	0.52
BMI, kg/m ² (mean ± s.d.)	25.9±4.9	25.9±5.1	25.8±5.2	1.0
Systolic Blood Pressure,mmHg (mean ± s.d.)	135.3±17.0	133.6±16.9	141.5±19.8	0.30
Diastolic Blood Pressure,mmHg (mean ± s.d.)	78.5±11.6	78.7±12.5	82.9±13.9	0.45

eGFR, mL/min per 1.73 m ²	74.8±19.6	72.5±18.5	74.3±15.3	0.65
Qualifying stroke:				
Cerebral hemisphere with cortical involvement	52 %	40 %	12 %	0.00
Cerebral hemisphere,subcortical only	16 %	26 %	24 %	0.13
Brainstem only	5 %	5 %	0 %	0.66
Cerebellum only	8 %	5 %	12 %	0.49
Multiple Locations	20 %	25 %	53 %	0.01
Chronic infarct on imaging (in addition to index stroke)	45 %	68 %	76 %	0.00
Hemorrhagic transformation	10 %	8 %	0 %	0.39
Evidence of old macrohemorrhage	5 %	5 %	6 %	0.98
Oral antithrombotic therapy use prior to qualifying stroke	0 %	0 %	0 %	1.00
Statin use prior to randomization	56 %	64 %	59 %	0.53
Treated with intravenous tPA for qualifying stroke	14 %	9 %	0 %	0.17
Treated with endovascular intervention	4 %	4 %	0 %	0.68
Functional measures at randomization:				
EQ-5D (median, IQR)	75.0 (60.0, 90.0)	75.0 (60.0, 85.0)	70.0(70.0, 85.0)	0.45
MoCA (median, IQR)	24.0 (21.0, 27.0)	23.0 (20.0, 26.0)	23.0(22.0, 27.0)	0.13
NIHSS score at randomization (median, IQR)	0.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0(0.0, 1.0)	0.50
mRS at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (1.0, 2.0)	2.0(1.0, 2.0)	0.20
LV ejection fraction	63.1±8.9	65.7±7.3	62.2±9.7	0.05
LV hypertrophy	25 %	22 %	65 %	0.00
Functional outcomes at 12 months:				
EQ-5D (median, IQR)	80.0 (70.0, 90.0)	80.0 (60.0, 90.0)	80.0(60.0, 80.0)	0.28
MoCA (median, IQR)	25.0 (22.0, 27.0)	22.5 (20.0, 26.5)	23.0(20.0, 27.0)	0.24

Abbreviations: BMI, body mass index; CMB, cerebral microbleed; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of undetermined source; GI, gastrointestinal; IQR, interquartile range; LV, left ventricular; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; tPA, tissue plasminogen activator

eTable 3. Baseline Characteristics and MRI Findings by Cerebral Microbleed Topography

Characteristic	Strictly deep (N=213)	Strictly lobar (N=102)	Mixed (N=73)	pvalue
Age, years (mean ± s.d.)	70.0±9.1	68.3±10.4	69.6±9.4	0.35
Age<60 years	14 %	23 %	15 %	0.18
Male sex	60 %	62 %	62 %	0.93
Race:				
White only	49 %	63 %	41 %	0.01
Black only	2 %	2 %	5 %	0.31
East Asian only	44 %	23 %	44 %	0.00
Others (includes not reported/multiracial)	5 %	13 %	10 %	0.03
Global region:				
U.S.A. and Canada	12 %	25 %	16 %	0.01
Latin America	3 %	3 %	7 %	0.25
Western Europe	36 %	46 %	34 %	0.16
Eastern Europe	7 %	5 %	1 %	0.22
East Asia	43 %	21 %	41 %	0.00
Medical history:				
Hypertension	84 %	87 %	90 %	0.32
Diabetes mellitus	26 %	30 %	23 %	0.54
Current tobacco use	19 %	21 %	22 %	0.87
Coronary artery disease	6 %	12 %	5 %	0.15
Heart failure	2 %	4 %	3 %	0.56
Cancer	8 %	13 %	8 %	0.37
Prior stroke or TIA	23 %	22 %	23 %	0.93
Renal dysfunction	5 %	1 %	4 %	0.20
Liver disease	2 %	2 %	0 %	0.43
History of GI bleeding	1 %	2 %	5 %	0.13
CHADS2 (median, IQR)	3.0 (3.0, 4.0)	4.0 (3.0, 4.0)	3.0(3.0, 4.0)	0.73
CHA ₂ DS ₂ -VASc (median, IQR)	5.0 (4.0, 5.0)	5.0 (4.0, 6.0)	5.0(4.0, 6.0)	0.95
BMI, kg/m ² (mean ± s.d.)	26.1±4.8	26.3±4.3	25.7±5.5	0.69
Systolic Blood Pressure,mmHg (mean ± s.d.)	135.7±17.6	134.9±17.5	134.7±18.7	0.90
Diastolic Blood Pressure,mmHg (mean ± s.d.)	78.5±12.2	79.1±12.1	79.0±12.4	0.90

eGFR, mL/min per 1.73 m ²	76.3±21.2	73.5±18.1	72.4±20.3	0.29
Qualifying stroke:				
Cerebral hemisphere with cortical involvement	41 %	61 %	44 %	0.00
Cerebral hemisphere, subcortical only	22 %	10 %	22 %	0.02
Brainstem only	4 %	4 %	4 %	0.99
Cerebellum only	8 %	4 %	4 %	0.21
Multiple Locations	24 %	22 %	26 %	0.79
Chronic infarct on imaging (in addition to index stroke)	51 %	45 %	67 %	0.01
Hemorrhagic transformation	8 %	17 %	10 %	0.08
Evidence of old macrohemorrhage	7 %	3 %	4 %	0.28
Oral antithrombotic therapy use prior to qualifying stroke	0 %	0 %	0 %	1.00
Statin use prior to randomization	57 %	61 %	64 %	0.51
Treated with intravenous tPA for qualifying stroke	11 %	18 %	8 %	0.11
Treated with endovascular intervention	4 %	7 %	4 %	0.45
Functional measures at randomization:				
EQ-5D (median, IQR)	75.0 (64.0, 90.0)	75.0 (60.0, 90.0)	72.0(60.0, 85.0)	0.63
MoCA (median, IQR)	24.0 (21.0, 27.0)	25.0 (22.0, 27.0)	22.0(19.5, 26.5)	0.03
NIHSS score at randomization (median, IQR)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	1.0(0.0, 2.0)	0.32
mRS at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0(1.0, 2.0)	0.10
LV ejection fraction	63.6±8.2	61.8±8.9	64.7±7.8	0.11
LV hypertrophy	23 %	32 %	38 %	0.03
Functional outcomes at 12 months:				
EQ-5D (median, IQR)	80.0 (70.0, 90.0)	80.0 (70.0, 90.0)	70.0(50.0, 85.0)	0.12
MoCA (median, IQR)	25.0 (21.0, 27.0)	25.0 (22.0, 27.0)	23.5(20.0, 26.5)	0.51

Abbreviations: BMI, body mass index; CMB, cerebral microbleed; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of undetermined source; GI, gastrointestinal; IQR, interquartile range; LV, left ventricular; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; tPA, tissue plasminogen activator

eTable 4. Recurrent Stroke Subtypes by Cerebral Microbleed Status

Subgroup	ESUS (N=90)	Lacunar (N=27)	Cardioembolic (N=25)	Atherosclerosis (N=13)	Other (N=10)	pvalue
CMB Presence						
None CMB	79(2.4%)	21(0.6%)	21(0.6%)	12(0.4%)	7(0.2%)	
CMB	11(2.8%)	6(1.5%)	4(1.0%)	1(0.3%)	3(0.8%)	0.3154
CMB Count						
1-2 CMBs	5(2.3%)	1(0.5%)	3(1.4%)	1(0.5%)	1(0.5%)	
3 or more CMBs	3(2.9%)	3(2.9%)	0(0.0%)	0(0.0%)	0(0.0%)	0.4515
CMB topography						
Strictly deep/mixed CMBs	5(1.7%)	4(1.4%)	2(0.7%)	1(0.3%)	3(1.0%)	
Strictly lobar CMBs	6(5.9%)	2(2.0%)	2(2.0%)	0(0.0%)	0(0.0%)	0.3088

eTable 5. Efficacy in CMB Subgroups -- Recurrent Stroke

Subgroup	Rivaroxaban assigned (N=1872)		Aspirin-assigned (N=1827)		Hazard Ratio (95% CI)	pvalue (interaction)* *
	No. Rand	No. Events (Events Rate*)	No. Rand	No. Events (Events Rate*)		
CMB Presence						
None	1672	81 (5.0)	1632	80 (5.1)	0.99 (0.73, 1.35)	
CMB	200	18 (10.0)	195	11 (5.6)	1.68 (0.79, 3.56)	0.20
CMB burden						
No CMB	1672	81 (5.0)	1632	80 (5.1)	0.99 (0.73, 1.35)	
1-2 CMBs	104	6 (6.3)	114	6 (5.1)	1.19 (0.38, 3.69)	
3 or more CMBs	59	8 (15.4)	43	0 (0.0)		0.96
CMB topography						
No CMB	1672	81 (5.0)	1632	80 (5.1)	0.99 (0.73, 1.35)	
Strictly deep/mixed CMBs	152	12 (8.8)	134	5 (3.7)	2.27 (0.80, 6.44)	
Strictly lobar CMBs	45	6 (14.1)	57	6 (10.6)	1.36 (0.44, 4.22)	0.30

* Event rates reported in 100-Person Years

** Hazard Ratio, 95% CI, and p for interaction not reported if Hazard Ratio is ≥ 10 or cannot be computed

eTable 6. Efficacy in CMB Subgroups -- Ischemic Stroke

Subgroup	Rivaroxaban assigned (N=1872)		Aspirin-assigned (N=1827)		Hazard Ratio (95% CI)	pvalue (interaction)**
	No. Rand	No. Events (Events Rate*)	No. Rand	No. Events (Events Rate*)		
CMB Presence						
None	1672	75 (4.7)	1632	78 (4.9)	0.94 (0.69, 1.29)	
CMB	200	15 (8.3)	195	11 (5.6)	1.41 (0.65, 3.06)	0.3348
CMB Severity						
No CMB	1672	75 (4.7)	1632	78 (4.9)	0.94 (0.69, 1.29)	
1-2 CMBs	104	5 (5.2)	114	6 (5.1)	0.99 (0.30, 3.23)	
3 or more CMBs	59	6 (11.5)	43	0 (0.0)		0.9975
CMB topography						
No CMB	1672	75 (4.7)	1632	78 (4.9)	0.94 (0.69, 1.29)	
Strictly deep/mixed CMBs	152	10 (7.4)	134	5 (3.7)	1.90 (0.65, 5.57)	
Strictly lobar CMBs	45	5 (11.8)	57	6 (10.6)	1.13 (0.34, 3.71)	0.4603

* Event rates reported in 100-Person Years

** Hazard Ratio, 95% CI, and p for interaction not reported if Hazard Ratio is ≥ 10 or cannot be computed

eTable 7. Efficacy in CMB Subgroups --All-Cause Mortality

Subgroup	Rivaroxaban assigned (N=1872)		Aspirin-assigned (N=1827)		Hazard Ratio (95% CI)	pvalue (interaction)**
	No. Rand	No. Events (Events Rate*)	No. Rand	No. Events (Events Rate*)		
CMB Presence						
None	1672	24 (1.4)	1632	15 (0.9)	1.59 (0.83, 3.02)	
CMB	200	5 (2.6)	195	5 (2.5)	1.08 (0.31, 3.75)	0.5829
CMB Severity						
No CMB	1672	24 (1.4)	1632	15 (0.9)	1.59 (0.83, 3.02)	
1-2 CMBs	104	5 (5.0)	114	3 (2.5)	2.07 (0.49, 8.69)	
3 or more CMBs	59	0 (0.0)	43	0 (0.0)		0.9553
CMB topography						
No CMB	1672	24 (1.4)	1632	15 (0.9)	1.59 (0.83, 3.02)	
Strictly deep/mixed CMBs	152	3 (2.1)	134	3 (2.1)	1.07 (0.21, 5.34)	
Strictly lobar CMBs	45	2 (4.3)	57	2 (3.4)	1.29 (0.18, 9.17)	0.8675

* Event rates reported in 100-Person Years

** Hazard Ratio, 95% CI, and p for interaction not reported if Hazard Ratio is ≥ 10 or cannot be computed

eTable 8. Efficacy in CMB Subgroups—Intracerebral Hemorrhage

Subgroup	Rivaroxaban assigned (N = 1872)		Aspirin-assigned (N = 1827)		Hazard ratio (95% CI)	P value for interaction
	No. Rand	No. events (events rate) ^a	No. Rand	No. events (events rate) ^a		
CMB presence						
None	1672	6 (0.4)	1632	2 (0.1)	2.96 (0.60-14.66)	NA
CMB	200	3 (1.6)	195	1 (0.5)	3.12 (0.32-30.01)	.97
CMB burden						
None	1672	6 (0.4)	1632	2 (0.1)	2.96 (0.60-14.66)	NA
1-2	104	1 (1.0)	114	0 (0.0)		NA
3 or more	59	2 (3.5)	43	1 (2.4)	1.43 (0.13-15.82)	.89
CMB topography						
None	1672	6 (0.4)	1632	2 (0.1)	2.96 (0.60-14.66)	NA
Strictly deep/mixed	152	2 (1.4)	134	1 (0.7)	1.98 (0.18-21.92)	NA
Strictly lobar	45	1 (2.2)	57	0 (0.0)		.96

Abbreviations: CMB, cerebral microbleed; NA, not applicable.

^aEvent rates reported in 100-person years.