Supplementary Online Content

Hong K-S, Kwon SU, Lee SH, et al; Phase 2 Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients With Non-valvular Atrial Fibrillation (Triple AXEL) Study Group. Rivaroxaban vs warfarin sodium in the ultra-early period after atrial fibrillation—related mild ischemic stroke: a randomized clinical trial. *JAMA Neurol.* Published online September 11, 2017. doi:10.1001/jamaneurol.2017.2161

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

eTable 1. Inclusion and Exclusion Criteria

Inclusion criteria

- 1. Acute presumed cardioembolic stroke of mild to moderate severity or TIA that fulfills the following criteria
- 1) Ischemic stroke or TIA with acute ischemic lesion confirmed by DWI
- 2) Randomization within 5 days after symptom onset
- 3) Mild to moderate stroke severity defined by acute ischemic lesion on DWI less than 1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory, and 1/2 of one cerebellar hemisphere
- 2. Persistent or paroxysmal AF documented by one of followings
- 1) AF documented by 12-lead ECG or Holter within 30 days before randomization
- 2) Prior history of AF confirmed by the review of medical record
- 3. Age \geq 19 years
- 4. Written informed consent

Exclusion criteria

- 1. Significant hemorrhagic transformation (parenchymal hematoma type I or type II by the ECASS definition)
- 2. Mechanical heart valve requiring warfarin therapy
- 3. Stroke or TIA caused by presumed small vessel occlusion defined as <2.0 cm in largest dimension on DWI and in the distribution of the small, penetrating cerebral arteries
- 4. Renal impairment (CrCl <30 ml/min) or severe hepatic impairment
- 5. Active internal bleeding
- 6. History of symptomatic intracranial bleeding
- 7. History of major surgery or trauma within 30 days
- 8. History of clinically significant gastrointestinal bleeding within 6 months
- 9. Patients treated with intravenous tissue plasminogen activator or intra-arterial fibrinolysis within 48 hours and having significant hemorrhagic transformation or large acute ischemic lesion on DWI (>1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory, or 1/2 of one cerebellar hemisphere)
- 10. Severe aemia: Hb level <10 g/dL

- 11. Bleeding diathesis: platelet count <90,000/μl or PTINR >1.7
- 12. Uncontrolled hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg
- 13. Malignancy or other serious medical conditions with a life expectancy <6 months
- 14. Planned major surgery or invasive intervention
- 15. Treatment with a strong inhibitor of cytochrome P450 3A4, such as azole class of antifungal agents (ketoconazole, itraconazole, voriconazole, posaconazole) or protease inhibitors (ritonavir), within 4 days before randomization, or planned treatment during the study period
- 16. Treatment with a strong inducer of cytochrome P450 3A4 or P-gp, such as rifampicin /rifampin, phenytoin, phenobarbital, carbamazepine, Saint. John's Wort, within 4 days before randomization, or planned treatment during the study period
- 17. Anticipated long-term treatment with a non-steroidal anti-inflammatory drug
- 18. Alcohol or drug addiction
- 19. Contraindication to MRI
- 20. Pregnancy or breast-feeding
- 21. Allergy or contraindication to rivaroxaban, warfarin, heparin, or aspirin
- 22. Inability or unwillingness to comply with study-related procedures
- 23. Employees of the investigator or study center, with direct involvement in the current study
- 24. Women unwilling to continue contraception during the study period
- 25. Participation in other clinical trials within 3 months

eTable 2. Study Procedures

	Screening	Baseline	Day 5 ± 2	Week2	Week 4	Week5	Post study	Unscheduled
Criteria	(from Day -	(Day 1)		(Day 14 ±	(Day 30 ±	(Week4	visit ¹	visit ²
	5)			5)	5)	visit+7±1)		
Informed consent	•							
Demography	•							
Inclusion/Exclusion	•	•						
Past Medical	•							
History								
Vital sign	•				•			•
Laboratory test ³	•		•	•4	•	•5		•
Pregnancy test ⁶	•							
ECG	•							
Brain imaging ⁷	•				•			•
mRS	•				•			•
NIHSS	•				•			•
HAS-BLED,		•						
CHADS2-VASC								
Randomization ⁸		•						
Drug						-		
administration ⁹								
Drug compliance		•	•	•4	•			
Adverse event								•
monitoring								
Concomitant drug	•				—	•		•

- 1. Allow tele-monitoring (Day 44 ± 5)
- 2. Appropriate action performed at the discrete of physician
- 3. At screening, week 4: CBC, AST, ALT, BUN, Cr, PT, APTT, Na, K, Total cholesterol, hs-CRP, At screening: available laboratory test results performed at emergency room in advance to obtaining informed consent could be utilized, Day 5; PT, BUN, Cr (all subject in warfarin arm and subject with screening CrCl < 45ml/min in Rivaroxaban arm), Week 2; warfarin arm only: PT, BUN, Cr, Week 5; Rivaroxaban arm only: PT, BUN, Cr
- 4. Refers to Warfarin arm only
- 5. Refers to Rivaroxaban arm only (Week 5 visit will be performed on 7±1 days post Week 4 visit)
- 6. For women of childbearing age, HCG urine test
- 7. Screening; Patients who have baseline DWI, FLAIR, and GRE or SWI are eligible for this trial. At 4 weeks, follow-up MRI scan (including FLAIR and GRE or SWI) is required for all included patients., and the primary outcome will be assessed using the follow-up MRI scan. For patients who have clinical stroke or intracranial bleeding before the end of trial, MRI will be evaluated at the time of the clinical events. CT scan for outcome assessment will be allowed only for patients who are not able to perform MRI, but have a clinical stroke or symptomatic intracranial bleeding (when the patient's stroke or intracranial bleeding is too serious to perform MRI scan).
- 8. After completion of all study procedures scheduled at screening visit, randomization is possible on the screening day (Date of

	first drug administration will be regarded as Day 1)
9.	For Rivaroxaban arm; first 5 days of warfarin transition, Rivaroxaban will be coadministered with warfarin

eTable 3. Characteristics of Patients Included in Modified Intent-To-Treat Population (ITT) and Those Excluded From the ITT Population

	Modified ITT	Patients who were	Patients who
	population	randomized, but	were randomized
	(N=183)	did not receive	and received
		treatment	treatment, but did
		(N=7)	not undergo
			follow-up MRI
Age (years), mean (SD)	70.4 (10.4)	64.6 (7.7)	(N=5) 69.2 (6.1)
	· ·	` '	
Female, n (%)	76 (41.5)	3 (42.9)	4 (80.0%)
Onset to randomization	2.0 (2.0–3.0)	1.0 (1.0-2.0)	4.0 (3.0-5.0)
(day), median (IQR)	20(00 40)	20(0020)	20(1020)
NIHSS at randomization,	2.0 (0.0–4.0)	3.0 (0.0-3.0)	2.0 (1.0-3.0)
median (IQR) Initial DWI volume (cm ³),	3.5 (0.5-12.3)	0.0 (0.0-0.1)	0.0 (0.0-33.9)
median (IQR)*	3.3 (0.3-12.3)	0.0 (0.0-0.1)	0.0 (0.0-33.7)
Prestroke CHA ₂ DS ₂ -VASc			
score			
0	21 (11.5)	1 (16.7)	0 (0.0)
1	31 (16.9)	1 (16.7)	1 (20.0)
2	40 (21.9)	2 (33.3)	0 (0.0)
3	37 (20.2)	1 (16.7)	3 (60.0)
4	36 (19.7)	1 (16.7)	0 (0.0)
5	14 (7.7)	0 (0.0)	1 (20.0)
6	3 (1.6)	-	-
7	1 (0.5)	-	-
Mean (SD)	2.5 (1.6)	2.0 (1.4)	3.0 (1.4)
Prestroke HAS-BLED			
score			
0	28 (15.3)	2 (33.3)	1 (20.0)
1	90 (49.2)	3 (50.0)	3 (60.0)
2	50 (27.3)	1 (16.7)	1 (20.0)
3	13 (7.1)	-	-
4	2 (1.1)	-	-
Mean (SD)	1.3 (0.9)	0.8 (0.8)	1.0 (0.7)
Paroxysmal atrial	49 (26.8)	2 (28.6)	2 (40.0)
fibrillation, n (%)			
Prior VKA use [†]	75 (41.0)	3 (42.9)	4 (80.0)
Risk factor, n (%)			

Hypertension	117 (63.9)	4 (57.1)	3 (60.0)
Diabetes mellitus*	34 (18.6)	3 (42.9)	2 (40.0)
Hyperlipidemia	34 (18.6)	2 (28.6)	0 (0.0)
Coronary artery disease	25 (13.7)	0 (0.0)	1 (20.0)
Baseline neuroimaging, n (%)			
CT	130 (71.0)	4 (57.1)	4 (80.0)
MRI	183 (100.0)	7 (100.0)	5 (100.0)
DWI	182 (99.5)	7 (100.0)	5 (100.0)
FLAIR	182 (99.5)	7 (100.0)	5 (100.0)
GRE	166 (90.7)	7 (100.0)	4 (80.0)
SWI	18 (9.8)	0 (0.0)	1 (20.0)
Others	38 (20.8)	1 (14.3)	1 (20.0)
Blood pressure at entry (mm Hg), mean (SD)			
Systolic	130.0 (18.2)	122.6 (19.2)	129.6 (19.9)
Diastolic	77.1 (11.3)	77.7 (11.0)	77.4 (12.4)
Heart rate, mean (SD)	83.9 (22.9)	71.1 (13.9)	78.4 (7.0)
Serum creatinine (mg/dL), mean (SD)	0.89 (0.24)	0.92 (0.34)	0.76 (0.12)
Concomitant antiplatelet use	57 (31.1)	1 (14.3)	1 (20.0)
Single antiplatelet	48 (26.2)	0 (0.0)	0 (0.0)
Aspirin	36 (19.7)	0 (0.0)	0 (0.0)
Clopidogrel	9 (4.9)	0 (0.0)	0 (0.0)
Others	3 (1.6)	0 (0.0)	0 (0.0)
Dual antiplatelet	9 (4.9)	1 (14.3)	1 (20.0)

eTable 4. Sensitivity Analyses

1) Sensitivity analyses for the primary endpoint including all patients who received the study drug

	Rivaroxaban (N=98)	Warfarin (N=90)	<i>P</i> -value [†]	Risk Difference (95% CI)	Relative Risk (95% CI)
Scenario 1	50 (51.0)	50 (55.6)	0.53	-4.54 (-18.78 - 9.80)	0.92 (0.70 - 1.20)
Scenario 2	47 (48.0)	48 (53.3)	0.46	-5.37 (-19.60 - 9.01)	0.90 (0.68 - 1.19)

[†]P-value by Chi-square test

Scenario 1: All subjects who did not undergo follow-up MRI were assumed to have a primary outcome event

Scenario 2: All subjects who did not undergo follow-up MRI were assumed not to have a primary outcome event

2) Sensitivity analyses of the ITT population

Of the patients who were included in the ITT population and were evaluated for the primary endpoint (recurrent ischemic lesion or new intracranial hemorrhage), in the warfarin group, recurrent ischemic lesion on 4-week MRI was not evaluated in one patient (indicated as patient 1 in table below), and new intracranial hemorrhage on 4-week MRI was not evaluated in another patient (indicated as patient 2 in table below).

	Initial MRI	4-week	Finding	Decision
	obtained	MRI		
		obtained		
Patient	DWI	FLAIR,	No intracranial	Primary endpoint: no
1		GRE	bleeding on 4-	Recurrent ischemic lesion: not
			week GRE	evaluable

				New intracranial bleeding: no
Patient 2	DWI, FLAIR	FLAIR, GRE	New ischemic lesion on follow-	Primary endpoint: yes Recurrent ischemic lesion:
2	1 L/ tilk	GKL	up FLAIR	yes
				New intracranial bleeding: not
				evaluable

Therefore, in the warfarin group in Table 2, the percentage of recurrent stroke lesion was 35.6% (= $[31/87] \times 100$), and the percentage of intracranial hemorrhage on 4-week MRI was 28.7% (= $[25/87] \times 100$).

2-1) Sensitivity analyses for the primary endpoint

Intracranial	Rivaroxaba	Warfari	P-	Risk Difference	Relative Risk
hemorrhag	n group	n group	value†	(95% CI)	(95% CI)
e or	(N=95)	(N=88)			
recurrent					
ischemic					
lesion on					
4- week					
MRI					
(primary					
endpoint)					
Scenario 1	47 (49.5)	49	0.401	-6.21 (-20.63 -	0.89 (0.67 -
		(55.7)		8.36)	1.17)
Scenario 2	47 (49.5)	49	0.401	-6.21 (-20.63 -	0.89 (0.67 -
		(55.7)		8.36)	1.17)
Scenario 3	47 (49.5)	48	0.493	-5.07 (-19.52 -	0.91 (0.69 -
		(54.5)		9.49)	1.20)
Scenario 4	47 (49.5)	48	0.493	-5.07 (-19.52 -	0.91 (0.69 -
		(54.5)		9.49)	1.20)

[†]P-value by Chi-square test

Scenario 1: Assuming that the patient who were not evaluable for recurrent ischemic lesion had recurrent ischemic lesion and the other patient who were not evaluable for new intracranial hemorrhage had new intracranial hemorrhage.

Scenario 2: Assuming that the patient who were not evaluable for recurrent ischemic lesion had recurrent ischemic lesion and the other patient who were not evaluable for new

intracranial hemorrhage did not have new intracranial hemorrhage.

Scenario 3: Assuming that the patient who were not evaluable for recurrent ischemic lesion did not have recurrent ischemic lesion and the other patient who were not evaluable for new intracranial hemorrhage had new intracranial hemorrhage.

Scenario 4: Assuming that the patient who were not evaluable for recurrent ischemic lesion did not have recurrent ischemic lesion and the other patient who were not evaluable for new intracranial hemorrhage did not have new intracranial hemorrhage.

2-2) Sensitivity analyses for the secondary endpoint of recurrent ischemic lesion on 4week MRI in ITT population

Recurrent	Rivaroxaba	Warfarin	P-	Risk Difference	Relative Risk
ischemic	n group	group	value†	(95% CI)	(95% CI)
lesion on	(N=95)	(N=88)			
4- week					
MRI					
Scenario	28 (29.5)	32	0.321	-6.89 (-21.18 -	0.81 (0.53 -
1		(36.4)		7.70)	1.23)
Scenario	28 (29.5)	31	0.405	-5.75 (-20.06 -	0.84 (0.55 -
2		(35.2)		8.83)	1.27)

[†]P-value by Chi-square test

Scenario 1: Assuming that the patient who were not evaluable for recurrent ischemic lesion had recurrent ischemic lesion.

Scenario 2: Assuming that the patient who were not evaluable for recurrent ischemic lesion did not have recurrent ischemic lesion.

2-3) Sensitivity analyses for the secondary endpoint of new intracranial hemorrhage on 4-week MRI in ITT population

Intracranial	Rivaroxaba	Warfarin	P-value†	Risk Difference	Relative Risk
hemorrhage	n group	group		(95% CI)	(95% CI)
on 4- week	(N=95)	(N=88)			
MRI					
Scenario 1	30 (31.6)	26 (29.5)	0.766	2.03 (-12.44 -	1.07 (0.69 -
				16.50)	1.66)
Scenario 2	30 (31.6)	25 (28.4)	0.640	3.17 (-11.34 -	1.11 (0.71 -
				17.61)	1.73)

[†]P-value by Chi-square test

Scenario 1: Assuming that the patient who were not evaluable for new intracranial hemorrhage had new intracranial hemorrhage.

Scenario 2: Assuming that the patient who were not evaluable for new intracranial hemorrhage did not have new intracranial hemorrhage.

eTable 5. Endpoints in the Per-Protocol Population

	Rivaroxaba n group (N=93)	Warfari n group (N=87)	Risk differenc e (95% CI)	Relativ e risk (95% CI)	P value	Adjuste d relative risk (95% CI)	P value
Intracranial hemorrhage or recurrent ischemic lesion on 4- week MRI (primary endpoint)	46 (49.5)	47 (54.0)	-4.56 (-19.17– 10.15)	0.92 (0.69– 1.21)	0.5406	0.96 (0.72– 1.28)	0.792
Recurrent ischemic lesion on 4- week MRI	27 (29.0)	30 (34.9)	-5.85 (-20.33– 8.87)	0.83 (0.54– 1.28)	0.4011	0.86 (0.55– 1.32)	0.484
Intracranial hemorrhage on 4-week MRI	30 (32.3)	24 (27.9)	4.35 (-10.30– 18.90)	1.16 (0.74– 1.81)	0.5263	1.22 (0.77– 1.95)	0.396
Clinical recurrent ischemic stroke	0 (0)	1 (1.1)	-1.15 (-15.77– 13.49)	-	0.4833	-	-
Symptomatic hemorrhagic conversion or hemorrhagic stroke	0 (0)	0 (0)	-	-	>0.999	-	-
Major bleeding	1 (1.1)	0 (0)	1.08 (-13.58– 15.68)	-	>0.999	-	-
Systemic embolism	0 (0)	0 (0)	-	-	>0.999	-	-
Acute coronary syndrome	0 (0)	0 (0)	-	-	>0.999	-	-
Composite of stroke, MI, or vascular death	0 (0)	1 (1.1)	-1.15 (-15.77– 13.49)	-	0.4833	-	-
Composite of stroke, MI,	1 (1.1)	1 (1.1)	-0.07 (-14.72–	0.94 (0.06–	>0.999	-	-

vascular			14.54)	14.73)			
death, or							
major							
bleeding							
Composite of	0 (0)	1 (1.1)	-1.15	-	0.4833	-	-
clinical			(-15.8–				
ischemic			13.49)				
events							
Duration of	4.0 (2.0-	6.0	-	-	< 0.000	-	0.005
hospitalizatio	6.0)	(4.0-			1		1
n (days),		8.0)					
median							
(IQR)							
mRS 0-1 at 4	78 (83.9)	64	8.58	1.11	0.1547	1.04	0.754
weeks		(74.4)	(-6.16–	(0.96-		(0.82-	3
			23.00)	1.30)		1.31)	

Data are n (%) unless otherwise stated. MI=myocardial infarction Adjusted for age, sex, initial ischemic lesion volume on diffusion-weighted image, diabetes, prior vitamin K antagonist, concomitant antiplatelet use, and center

eTable 6. Characteristics of New Ischemic Lesion in the Modified ITT Population

	Rivaroxaban group (N=95)	Warfarin group (N=88)	P-value [†]					
Size in diameter >10 mm, n (%)	12 (12.6)	14 (15.9)	0.6370					
Multiplicity, n (%)	19 (20.0)	8 (9.2)	0.0405					
†n 1 1 n / 1:								

[†] *P*-value by Pearson's chi-square test

eTable 7. Characteristics of New Intracranial Hemorrhage in the Modified ITT Population

	Rivaroxaban group (N=95) Warfarin group (N=87)		P-value [†]
			0.1971
No HT	65 (68.4)	62 (71.3)	
HT type I	18 (18.9)	10 (11.5)	
HT type II	11 (11.6)	10 (11.5)	
PH	1 (1.1)	5 (5.7)	

[†] *P*-value by Fisher's exact test to compare the whole distribution between the two groups

HT=hemorrhage infarction. PH=parenchymal haematoma.

HT type I: small hyperdense petechiae; HT type II: more confluent hyperdensity throughout the infarct zone without mass effect; PH: homogeneous hyperdensity with mass effect.

In the warfarin group, there was one missing value because one patient had only follow-up GRE without initial GRE/SWI.

eTable 8. Subgroup Analysis for Primary Endpoint in the Modified ITT Population

	N	Rivaroxa ban	Warfarin	<i>P</i> -value [†]	Relative Risk (95% CI)	<i>P</i> -value [‡]
Age						0.9626
≤70 yr	95	29 (54.7)	26 (61.9)	0.4810	0.88 (0.63–1.24)	
>70 yr	88	18 (42.9)	22 (47.8)	0.6401	0.90 (0.56–1.42)	
Sex						0.2534
Male	10 7	27 (49.1)	32 (61.5)	0.1957	0.80 (0.57–1.13)	
Female	76	20 (50.0)	16 (44.4)	0.6282	1.13 (0.70–1.82)	
Prior VKA use						0.1928
No	10 8	25 (44.6)	30 (57.7)	0.1753	0.77 (0.53–1.12)	
Yes	75	22 (56.4)	18 (50.0)	0.5783	1.13 (0.74–1.73)	
Prestroke CHA ₂ DS ₂ - VASc						0.8027
≤1	11 8	33 (55.9)	35 (59.3)	0.7095	0.94 (0.69–1.29)	
≥2	65	14 (38.9)	13 (44.8)	0.6291	0.87 (0.49–1.54)	
Prestroke HAS-BLED						0.8329
≤2	92	25 (61.0)	33 (64.7)	0.7126	0.94 (0.69–1.29)	
≥3	91	22 (40.7)	15 (40.5)	0.9848	1.00 (0.61–1.67)	
Baseline DWI volume						0.3007
≤3.53 cm ³	91	26 (49.1)	17 (44.7)	0.6840	1.10 (0.70–1.72)	
>3.53 cm ³	92	21 (50.0)	31 (62.0)	0.2475	0.81 (0.56–1.17)	
Concomitant antiplatelet use						0.6851

No	12 6	31 (50.8)	35 (53.8)	0.7339	0.94 (0.68–1.32)	
Yes	57	16 (47.1)	13 (56.5)	0.4832	0.83 (0.50–1.38)	
Creatinine Clearance						0.6601
<50 mL/min	35	5 (31.3)	8 (42.1)	0.5079	0.74 (0.30–1.82)	
≥50 mL/min	14 8	42 (53.2)	40 (58.0)	0.5573	0.92 (0.69–1.22)	

[†] P-value by Chi-square test or Fisher's exact test as appropriate ‡ P-value for interaction effect

VKA=vitamin K antagonist

eTable 9. Subgroup Analysis for Recurrent Ischemic Lesion in the Modified ITT Population

	N	Rivaroxa ban	Warfarin	P- value [†]	Relative Risk (95% CI)	<i>P</i> -value [‡]
Age						0.4019
≤70 yr	94	17 (32.1)	19 (46.3)	0.1582	0.69 (0.41–1.15)	
>70 yr	88	11 (26.2)	12 (26.1)	0.9912	1.00 (0.50–2.03)	
Sex						0.0587
Male	10 6	14 (25.5)	22 (43.1)	0.0548	0.59 (0.34–1.02)	
Female	76	14 (35.0)	9 (25.0)	0.3434	1.40 (0.69–2.84)	
Prior VKA use						0.0422
No	10 7	12 (21.4)	20 (39.2)	0.0447	0.55 (0.30–1.00)	
Yes	75	16 (41.0)	11 (30.6)	0.3453	1.34 (0.72–2.50)	
Prestroke CHA ₂ DS ₂ -VASc						0.3698
≤1	11 8	20 (33.9)	21 (35.6)	0.8467	0.95 (0.58–1.56)	
≥2	64	8 (22.2)	10 (35.7)	0.2337	0.62 (0.28–1.37)	
Prestroke HAS-BLED						0.3152
≤2	91	12 (29.3)	21 (42.0)	0.2088	0.70 (0.39–1.24)	
≥3	91	16 (29.6)	10 (27.0)	0.7872	1.10 (0.56–2.14)	
Baseline DWI volume						0.5328
≤3.53 cm ³	91	17 (32.1)	13 (34.2)	0.8308	0.94 (0.52–1.69)	
>3.53 cm ³	91	11 (26.2)	18 (36.7)	0.2819	0.71 (0.38–1.33)	

Concomitant antiplatelet use						0.7910
No	12 6	17 (27.9)	23 (35.4)	0.3651	0.79 (0.47–1.33)	
Yes	56	11 (32.4)	8 (36.4)	0.7569	0.89 (0.43–1.86)	
Creatinine Clearance						0.5057
<50 ml/min	35	4 (25.0)	4 (21.1)	1.0000	1.19 (0.35–4.01)	
≥50 ml/min	14 7	24 (30.4)	27 (39.7)	0.2362	0.77 (0.49–1.19)	

[†] P-value by Chi-square test or Fisher's exact test as appropriate ‡ P-value for interaction effect

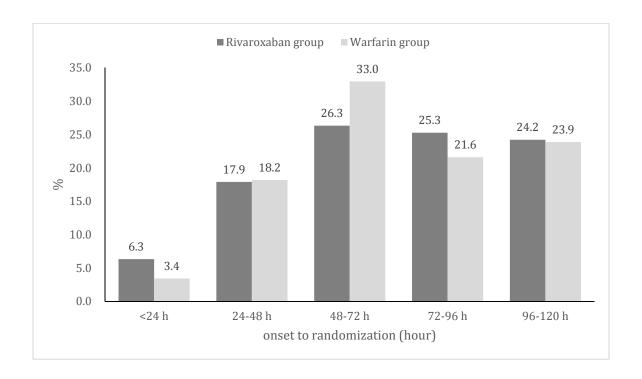
eTable 10. Subgroup Analysis for Intracranial Bleeding in the Modified ITT Population

	N	Rivaroxab an	Warfarin	P-value [†]	Relative Risk (95% CI)	P-value [‡]
Age						0.0669
≤70 yr	94	22 (41.5)	11 (26.8)	0.1392	1.55 (0.85–2.81)	
>70 yr	88	8 (19.0)	14 (30.4)	0.2179	0.63 (0.29–1.34)	
Sex						0.5043
Male	10 6	20 (36.4)	15 (29.4)	0.4470	1.24 (0.71–2.14)	
Female	76	10 (25.0)	10 (27.8)	0.7836	0.90 (0.42–1.91)	
Prior VKA use						0.7853
No	10 7	19 (33.9)	15 (29.4)	0.6162	1.15 (0.66–2.02)	
Yes	75	11 (28.2)	10 (27.8)	0.9672	1.02 (0.49–2.10)	
Prestroke CHA ₂ DS ₂ - VASc						0.7578
≤1	11 7	22 (37.3)	20 (34.5)	0.7518	1.08 (0.67–1.76)	
≥2	65	8 (22.2)	5 (17.2)	0.6178	1.29 (0.47–3.52)	
Prestroke HAS-BLED						0.4485
≤2	91	19 (46.3)	17 (34.0)	0.2309	1.36 (0.82–2.26)	
≥3	91	11 (20.4)	8 (21.6)	0.8853	0.94 (0.42–2.12)	
Baseline DWI volume						0.1944
≤3.53 cm ³	91	15 (28.3)	6 (15.8)	0.1624	1.79 (0.77–4.19)	
>3.53 cm ³	91	15 (35.7)	19 (38.8)	0.7635	0.92 (0.54–1.58)	
Concomitant antiplatelet use						0.3092
No	12 5	18 (29.5)	20 (31.3)	0.8324	0.94 (0.55–1.61)	
Yes	57	12 (35.3)	5 (21.7)	0.2724	1.62 (0.66–3.99)	
Creatinine Clearance						0.1205

<50 ml/min	35	1 (6.3)	5 (26.3)	0.1874	0.24 (0.03–1.83)	
≥50 ml/min	14 7	29 (36.7)	20 (29.4)	0.3494	1.25 (0.78–1.99)	

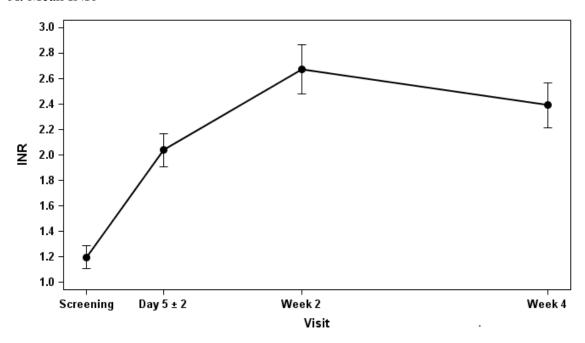
[†] P-value by Chi-square test or Fisher's exact test as appropriate ‡ P-value for interaction effect

eFigure 1. Onset to Randomization



eFigure 2. INR Values in the Warfarin Group

A. Mean INR



B. Proportion of achieving target INR of 2.0-3.0

