Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Table of Contents

List of Investigators 3
ELAN Trial Organization 8
Steering Committee 8
Data Safety Monitoring Board 8
Clinical Event Adjudication 8
Central Imaging Assessment 8
Neuro Clinical Trial Unit 8
Data Monitoring And Management 8
Additional Details About Statistical Analyses 10
Statistical Software Used and Quality Control 10
Components of Secondary Outcome: Major Extracranial Bleeding 10
Other Outcomes of Interest 10
Multiple Imputation Details 10
Sensitivity Analyses 11
Definition of Per-Protocol Population 11
Deviations from the Statistical Analysis Plan 12
Supplemental Tables 13
Table S1. Additional Baseline Characteristics. 13
Table S2. Procedural Characteristics. 18
Table S3. Additional Details on Adverse Events. 21
Table S4. Additional Details on Serious Adverse Events (SAEs). 35
Table S5. MedDRA coded Serious Adverse Events. 38
Table S6. Additional Secondary Outcomes and Other Outcomes of Interest. 41
Table S7. Sensitivity Analysis of Primary Outcome. 45
Table S8. Time-to-event Analysis. 46
Table S9. Results of Per-Protocol Analyses. 48
Table S10. Protocol Deviations 53
Table S11. Additional Results of Subgroup Analysis. 55
Table S12. Representativeness of Study Participants. 57
Table S13. Stroke Size Classification. 59
Supplemental Figures 60
Figure S1 Cumulative Probabilities of Risk Difference of the Composite Outcome (A) and its Components (B) between Early versus Late DOAC Initiation 60

Figure S2. Subgroup Analyses of the Composite Outcome at 30 (A) and 90 (B) Days. 61
Figure S3. Cumulative Incidence Plot of the Primary Outcome. 63
Figure S4. Cumulative Incidence Plots of Individual Components of the Composite Outcome. 64
Figure S5. Stroke Size Classification. 69
Figure S6. Complete Flowchart. 70
Clinical Event Committee: Event Adjudication Forms 71
References 88

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Additional Details About Statistical Analyses

Statistical Software Used and Quality Control

All analyses were performed using the statistical software R 4.2.1 or newer (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). A second statistician reproduced the primary analysis using Stata version 17.0 (StataCorp, TX, USA).

Components of Secondary Outcome: Major Extracranial Bleeding

- Decrease in hemoglobin of ≥2 g/dl over a 24-h period or
- Transfusion of ≥2 units of packed red blood cells and
- Occurring in a critical part of the body.

Other Outcomes of Interest

The other outcomes of interest included the composite of major cardiovascular events (defined as stroke, myocardial infarction, heart failure, or cardiovascular death), transient ischemic stroke, and undetermined stroke. The outcome ‘silent brain lesions’; defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without cerebral infarction, is not shown due to the low number of CT/MRI scans available.

Time-to-event analysis

The time-to-event analysis was performed on the composite primary outcome and its components at 30 and 90 days. Other secondary outcomes and outcomes of interest were not analyzed since only incomplete information about the date of the event was available.

Multiple Imputation Details

Multiple imputation for missing primary outcome data was performed based on the randomized treatment group and the following variables: sex; age; National Institutes of Health Stroke Scale (NIHSS); stroke classification; previous stroke, transient ischemic attack, or systemic embolism; hypertension; diabetes; previous myocardial infarction or heart failure (New York Heart Association (NYHA) Classification); and left ventricular ejection fraction <35%. The mice package in R for missing data imputation and model checking was used. The method used for multiple imputation is based on Fully Conditional Specification. The imputation of the primary outcome was performed using the Lasso select + logistic regression and 50 multiple imputations were performed. The model estimation was then performed using the same method as used for the primary analysis.

Sensitivity Analyses

We performed three different sensitivity analyses for the primary analysis of the primary endpoint:

- Unadjusted risk difference with 95% confidence intervals using the Miettinen & Nurminen form.[1]
- Penalized likelihood method according to King & Zeng[2] and implemented in the Zelig package using the relogit command in R. The model has the following form:

  $$logit\left(p(Y_j = 1)\right) = a + \beta Treat_j + \boldsymbol{\gamma SF_j}$$

  where *Treat* is an index variable denoting the treatment randomized or received (depending on the set used and the estimand targeted) and ***SF*** is a matrix with the stratification factors (except the site). The estimated odds ratio and standard error are then translated into a risk difference with a 95% confidence interval.
- Analysis without multiple imputation.

Definition of Per-Protocol Population

The per-protocol population comprised all enrolled patients with no major protocol violation. These included:

- violation of inclusion or exclusion criteria, or
- randomization outside the time window i.e., > 48 hours from symptom onset for minor and moderate strokes and < 120 hours or > 168 hours from symptom onset for major strokes, or
- treatment received different than treatment assigned.

  Definition of treatment received:

	If treatment is initiated (hours after onset of ischemic stroke)	**Treatment received**
Minor stroke	≤ 48 hours	Early treatment
	> 48 hours or later	Late treatment
	> 336 hours, unless (earlier) treatment is contraindicated	Major protocol deviation
Moderate stroke	≤ 84 hours	Early treatment
	> 85 hours or later	Late treatment
	> 336 hours, unless (earlier) treatment is contraindicated	Major protocol deviation
Major stroke	≤120 hours (5th day)	Protocol violation
	> 120 and ≤ 216 hours (6th day to 9th day)	Early treatment
	> 216 hours (after the 10th day)	Late treatment
	> 336 hours, unless (earlier) treatment is contraindicated	Major protocol deviation

- Outcome assessment outside the specified time window (i.e., 30 ± 3 days and 90 ± 7 days after randomization for visits 7 and 8, respectively).

Deviations from the Statistical Analysis Plan

- The statistical analysis plan specified a penalized logistic regression according to the Zelig package. Due to its generally better properties, this was replaced by the method described by Firth.[3] The originally specified approach is now reported as sensitivity analysis.
- The analysis of the secondary outcomes and other outcomes of interest was performed following the same principle as for the primary analysis, using a penalized logistic regression (the statistical analysis plan specified a mixed-effects model).
- In the subgroup analyses, the subgroup trial site was replaced with the subgroup country due to the large number of trial sites.
- Definition of per-protocol analysis (PP set): Due to possible bias in the definition of the per-protocol analysis, the following considerations were specified: a) if treatment started too late (over 336 h) but an event caused this delay, the patient was not excluded from the PP set; b) this applies also for the crossovers – if the crossover was caused by an event that led to a delay, the patient was not excluded from the PP set; c) the visit window was reconsidered: the exclusion for violating the time window was considered if the visit at 30 days after randomization was done too early and no later visit was made, and for visit 8 if the visit took place earlier than 83 days after randomization.
- Additional sensitivity analyses were done for binary outcomes to account for competing events where risk differences and odds ratios were derived from the non-parametric Aalen-Johansen estimator taking competing events (death without prior event) into account.

Supplemental Tables

Table S1. Additional Baseline Characteristics.

	Early Treatment (N=1006)	Late Treatment (N=1007)
Additional characteristics		
Weight – kg (IQR)	75 (65–87)	75 (65–85)
Blood pressure systolic – mmHg (IQR)	138 (124–152)	137 (124–151)
Blood pressure diastolic – mmHg (IQR)	79 (70–87)	79 (70–88)
Heart rate at rest – beats/min (IQR)	77 (66–89)	77 (65–90)
Body temperature – °C (IQR)	37 (36–37)	37 (36–37)
Additional medical history information		
Left ventricular ejection fraction <35% – no. (%)	374 (37.2)	395 (39.2)
no	374 (37.2)	395 (39.2)
yes	45 (4.5)	42 (4.2)
unknown	587 (58.3)	570 (56.6)
Peripheral artery disease – no. (%)		
no	938 (93.2)	927 (92.1)
yes	34 (3.4)	47 (4.7)
unknown	34 (3.4)	33 (3.3)
Large vessel diseases of supraaortic vessels – no. (%)		
no	900 (89.5)	902 (89.6)
yes	50 (5.0)	54 (5.4)

unknown	56 (5.6)	51 (5.1)
Mitral stenosis – no. (%)		
no	914 (90.9)	940 (93.3)
yes	10 (1.0)	14 (1.4)
unknown	82 (8.2)	53 (5.3)
Dyslipidemia – no. (%)		
no	537 (53.4)	557 (55.3)
yes	439 (43.6)	422 (41.9)
unknown	30 (3.0)	28 (2.8)
Sleep disordered breathing – no. (%)		
no	824 (81.9)	844 (83.8)
yes	38 (3.8)	40 (4.0)
unknown	144 (14.3)	123 (12.2)
History of myocardial infarction – no. (%)		
no	916 (91.1)	909 (90.3)
yes	80 (8.0)	87 (8.6)
unknown	10 (1.0)	11 (1.1)
History of heart failure according to NYHA Classification – no. (%)		
no	873 (86.8)	877 (87.1)
yes	65 (6.5)	61 (6.1)
unknown	68 (6.8)	69 (6.9)
Smoking status – no. (%)		

Non-smoker	703 (69.9)	705 (70.0)
Current smoker	103 (10.2)	84 (8.3)
Former smoker	147 (14.6)	158 (15.7)
Unknown	53 (5.3)	60 (6.0)
Medication at screening		
Aspirin – no. (%)	457 (45.4)	545 (54.1)
Other antiplatelet – no. (%)	61 (6.1)	65 (6.5)
Clopidogrel – no. (%)	57 (93.4)	59 (90.8)
Prasugrel – no. (%)	0 (0.0)	0 (0.0)
Ticagrelor – no. (%)	1 (1.6)	0 (0.0)
Other – no. (%)	0 (0.0)	4 (6.2)
Thrombosis prophylaxis – no. (%)	292 (29.0)	376 (37.3)
Heparin, prophylactic – no. (%)	45 (15.4)	54 (14.4)
Low-molecular-weight heparin, prophylactic – no. (%)	229 (78.4)	291 (77.4)
Other thrombosis prophylaxis – no. (%)	16 (5.5)	21 (5.6)
Lab values		
Anti-IIa: not applicable – no. (%)	1004 (99.8)	1005 (99.8)
Anti-IIa – ng/ml (IQR)	31 (12, 49)	20 (20, 20)
Thrombin time: Not applicable – no. (%)	897 (89.2)	894 (88.8)
Thrombin time – sec (IQR)	16 (13, 18)	15 (13, 18)
Anti-Xa: not applicable – no. (%)	975 (96.9)	960 (95.3)

Anti-Xa – ng/ml (IQR)	36 (25, 61)	30 (13, 40)
Platelet count – cells/mm^3 (IQR)	218,000 (182,000, 261,000)	215,000 (177,000, 257,000)
Hemoglobin – g/dl (IQR)	14 (12, 15)	14 (12, 15)
INR – (IQR)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)
Creatinine clearance – ml/min (IQR)	71 (60, 86)	69 (57, 86)
Imaging		
Most recent scan before randomization (magnetic resonance imaging) – no. (%)	433 (43.0)	427 (42.4)
Middle cerebral artery (MCA) – no. (%)	707 (70.3)	696 (69.1)
Side – no. (%)		
left	356 (50.4)	329 (47.3)
right	325 (46.0)	338 (48.6)
both	26 (3.7)	29 (4.2)
Anterior cerebral artery (ACA) – no. (%)	50 (5.0)	53 (5.3)
Side – no. (%)		
left	27 (54.0)	30 (56.6)
right	19 (38.0)	20 (37.7)
both	4 (8.0)	3 (5.7)
Posterior cerebral artery (PCA) – no. (%)	139 (13.8)	147 (14.6)
Side – no. (%)		

left	64 (46.0)	72 (49.0)
right	60 (43.2)	59 (40.1)
both	15 (10.8)	16 (10.9)
Brainstem – no. (%)	46 (4.6)	39 (3.9)
Side – no. (%)		
left	21 (45.7)	16 (41.0)
right	18 (39.1)	14 (35.9)
both	7 (15.2)	9 (23.1)
Cerebellum – no. (%)	90 (8.9)	105 (10.4)
Side – no. (%)		
left	46 (51.1)	42 (40.0)
right	34 (37.8)	47 (44.8)
both	10 (11.1)	16 (15.2)
Basal ganglia – no. (%)	91 (9.0)	75 (7.4)
Side – no. (%)		
left	42 (46.2)	36 (48.0)
right	47 (51.6)	36 (48.0)
both	2 (2.2)	3 (4.0)
Anterior choroidal artery – no. (%)	16 (1.6)	15 (1.5)
Side – no. (%)		
left	7 (43.8)	10 (66.7)
right	9 (56.3)	5 (33.3)
both	0 (0.0)	0 (0.0)

IQR interquartile range. NYHA New York Heart Association.

Table S2. Procedural Characteristics.

	Early Treatment (N =1006)	Late Treatment (N = 1007)
DOAC was started within the correct time window according to the trial allocation – no. (%)	951 (94.7)	933 (93.1)
Did the patient need a dose reduction according to the summary of product characteristics? – no. (%)		
no	819 (81.6)	806 (80.4)
yes	182 (18.1)	191 (19.1)
missing	3 (0.3)	5 (0.5)
Type of DOAC – no dose reduction – no. (%)		
Rivaroxaban 20 mg once a day	43 (5.3)	52 (6.5)
Dabigatran 150 mg twice a day	127 (15.5)	124 (15.4)
Apixaban 5 mg twice a day	550 (67.2)	526 (65.3)
Edoxaban 60 mg once a day	95 (11.6)	98 (12.2)
missing	4 (0.5)	6 (0.7)
Type of DOAC – dose reduction, yes – no. (%)		
Dabigatran 110 mg twice a day	42 (23.1)	49 (25.7)
Apixaban 2.5 mg twice a day	80 (44.0)	87 (45.5)
Edoxaban 30 mg once a day	58 (31.9)	51 (26.7)

Rivaroxaban 15 mg once a day (protocol 2.0 only)	2 (1.1)	3 (1.6)
missing	0 (0.0)	1 (0.5)
Reason for dose reduction (dabigatran) age ≥ 80 years – no. (%)		
no	8 (19.0)	7 (14.3)
yes	33 (78.6)	42 (85.7)
missing	1 (2.4)	0 (0.0)
Reason for dose reduction (dabigatran) patient receives concomitant verapamil – n (%)		
no	40 (95.2)	48 (98.0)
yes	0 (0.0)	1 (2.0)
missing	2 (4.8)	0 (0.0)
Reason for reduction: age ≥ 80 years and weight ≤ 60 kg – no. (%)	57 (71.2)	55 (63.2)
Reason for dose reduction (Edoxaban) weight ≤ 60kg – n (%)	42 (72.4)	35 (68.6)
Reason for reduction: concomitant use of inhibitors – no. (%)	0 (0.0)	1 (2.0)
Was participant hospitalized at the time of DOAC initiation? – no. (%)		

no	93 (9.3)	266 (26.5)
yes	910 (90.6)	730 (72.9)
missing	1 (0.1)	6 (0.6)
DOAC, direct oral anticoagulants.		

Table S3. Additional Details on Adverse Events.

Overall Study Period†	Total (N=1940)	Early Treatment (N = 947)	Late Treatment (N = 993)
Event	No. of Patients with Event (%)	No. of Patients with Event (%)	No. of Patients with Event (%)
Any serious adverse event (SAE)‡	289 (14.9)	132 (13.9)	157 (15.8)
Any adverse event (AE)	975 (50.3)	446 (47.1)	529 (53.3)
COVID-19 positive†	31 (2.8)	13 (2.5)	18 (3.1)
Symptomatic	19 (61.3)	8 (61.5)	11 (61.1)
General events			
Cerebral infarction	32 (1.6)	13 (1.4)	19 (1.9)
Hemorrhage, intracranial	10 (0.5)	4 (0.4)	6 (0.6)
Pulmonary embolism	2 (0.1)	1 (0.1)	1 (0.1)
Myocardial infarction	4 (0.2)	3 (0.3)	1 (0.1)
Multiple organ dysfunction syndrome§	1 (0.1)	1 (0.1)	0 (0.0)

Infections			
Urinary tract infection	131 (6.8)	69 (7.3)	62 (6.2)
Pneumonia	82 (4.2)	38 (4.0)	44 (4.4)
Sepsis§	8 (0.4)	1 (0.1)	7 (0.7)
Systemic inflammatory response syndrome§	4 (0.2)	0 (0.0)	4 (0.4)
Neurological deficits			
Aphasia, motor	302 (15.6)	140 (14.8)	162 (16.3)
Aphasia, sensory	151 (7.8)	70 (7.4)	81 (8.2)
Hemiparesis, left	272 (14.0)	126 (13.3)	146 (14.7)
Hemiparesis, right	247 (12.7)	110 (11.6)	137 (13.8)
Neglect	159 (8.2)	66 (7.0)	93 (9.4)
Visual field disorders	162 (8.4)	69 (7.3)	93 (9.4)
Cognitive impairment	237 (12.2)	105 (11.1)	132 (13.3)
Persistent vegetative state	6 (0.3)	3 (0.3)	3 (0.3)
Seizure	17 (0.9)	6 (0.6)	11 (1.1)

Delirium	42 (2.2)	19 (2.0)	23 (2.3)
MedDRA coded AE ∫			
Blood and lymphatic system disorders	6 (0.3)	3 (0.3)	3 (0.3)
Cardiac disorders	50 (2.6)	23 (2.4)	27 (2.7)
Congenital, familial and genetic disorders	1 (0.1)	1 (0.1)	0 (0.0)
Endocrine disorders	2 (0.1)	1 (0.1)	1 (0.1)
Eye disorders	3 (0.2)	2 (0.2)	1 (0.1)
Gastrointestinal disorders	38 (2.0)	15 (1.6)	23 (2.3)
General disorders and administration site conditions	38 (2.0)	16 (1.7)	22 (2.2)
Hepatobiliary disorders	1 (0.1)	0 (0.0)	1 (0.1)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	27 (1.4)	17 (1.8)	10 (1.0)

Injury, poisoning and procedural complications	10 (0.5)	2 (0.2)	8 (0.8)
Investigations	8 (0.4)	5 (0.5)	3 (0.3)
Metabolism and nutrition disorders	17 (0.9)	7 (0.7)	10 (1.0)
Musculoskeletal and connective tissue disorders	25 (1.3)	8 (0.8)	17 (1.7)
Neoplasms – benign, malignant and unspecified (including cysts and polyps)	7 (0.4)	5 (0.5)	2 (0.2)
Nervous system disorders	82 (4.2)	39 (4.1)	43 (4.3)
Psychiatric disorders	33 (1.7)	18 (1.9)	15 (1.5)
Renal and urinary disorders	22 (1.1)	15 (1.6)	7 (0.7)
Reproductive system and breast disorders	2 (0.1)	1 (0.1)	1 (0.1)

Respiratory, thoracic and mediastinal disorders	26 (1.3)	16 (1.7)	10 (1.0)
Skin and subcutaneous tissue disorders	10 (0.5)	3 (0.3)	7 (0.7)
Surgical and medical procedures	4 (0.2)	2 (0.2)	2 (0.2)
Vascular disorders	66 (3.4)	27 (2.9)	39 (3.9)
Up to day 30¶	Total (N=1888)	Early Treatment (N = 915)	Late Treatment (N = 973)
Event	No. of Patients with Event (%)	No. of Patients with Event (%)	No. of Patients with Event (%)
Any AE	870 (46.1)	393 (43.0)	477 (49.0)
COVID-19 positive†	17 (1.8)	9 (2.0)	8 (1.6)
Symptomatic	13 (76.5)	7 (77.8)	6 (75.0)
General events			

Cerebral infarction	21 (1.1)	9 (1.0)	12 (1.2)
Hemorrhage, intracranial	9 (0.5)	4 (0.4)	5 (0.5)
Pulmonary embolism	2 (0.1)	1 (0.1)	1 (0.1)
Myocardial infarction	3 (0.2)	2 (0.2)	1 (0.1)
Multiple organ dysfunction syndrome§	0 (0.0)	0 (0.0)	0 (0.0)
Infections			
Urinary tract infection	89 (4.7)	52 (5.7)	37 (3.8)
Pneumonia	62 (3.3)	31 (3.4)	31 (3.2)
Sepsis§	7 (0.4)	0 (0.0)	7 (0.7)
Systemic inflammatory response syndrome§	2 (0.1)	0 (0.0)	2 (0.2)
Neurological deficits			
Aphasia, motor	266 (14.1)	120 (13.1)	146 (15.0)
Aphasia, sensory	137 (7.3)	65 (7.1)	72 (7.4)
Hemiparesis, left	245 (13.0)	112 (12.2)	133 (13.7)

Hemiparesis, right	226 (12.0)	104 (11.4)	122 (12.6)
Neglect	146 (7.7)	60 (6.6)	86 (8.8)
Visual field disorders	144 (7.6)	59 (6.4)	85 (8.7)
Cognitive impairment	184 (9.7)	84 (9.2)	100 (10.3)
Persistent vegetative state	5 (0.3)	3 (0.3)	2 (0.2)
Seizure	9 (0.5)	3 (0.3)	6 (0.6)
Delirium	33 (1.7)	18 (2.0)	15 (1.5)
MedDRA coded AE ∫			
Blood and lymphatic system disorders	3 (0.2)	2 (0.2)	1 (0.1)
Cardiac disorders	21 (1.1)	9 (1.0)	12 (1.2)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	1 (0.1)	0 (0.0)	1 (0.1)
Eye disorders	2 (0.1)	1 (0.1)	1 (0.1)
Gastrointestinal disorders	21 (1.1)	7 (0.8)	14 (1.4)

General disorders and administration site conditions	16 (0.8)	7 (0.8)	9 (0.9)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	13 (0.7)	8 (0.9)	5 (0.5)
Injury, poisoning and procedural complications	6 (0.3)	2 (0.2)	4 (0.4)
Investigations	5 (0.3)	3 (0.3)	2 (0.2)
Metabolism and nutrition disorders	8 (0.4)	3 (0.3)	5 (0.5)
Musculoskeletal and connective tissue disorders	11 (0.6)	3 (0.3)	8 (0.8)
Neoplasms – benign, malignant and unspecified (including cysts and polyps)	3 (0.2)	3 (0.3)	0 (0.0)
Nervous system disorders	46 (2.4)	18 (2.0)	28 (2.9)

Psychiatric disorders	17 (0.9)	11 (1.2)	6 (0.6)
Renal and urinary disorders	13 (0.7)	8 (0.9)	5 (0.5)
Reproductive system and breast disorders	2 (0.1)	1 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	13 (0.7)	7 (0.8)	6 (0.6)
Skin and subcutaneous tissue disorders	2 (0.1)	1 (0.1)	1 (0.1)
Surgical and medical procedures	2 (0.1)	1 (0.1)	1 (0.1)
Vascular disorders	40 (2.1)	16 (1.7)	24 (2.5)
Between day 30 and day 90¶¶	Total (N=1840)	Early Treatment (N = 895)	Late Treatment (N = 945)
Event	No. of Patients with Event (%)	No. of Patients with Event (%)	No. of Patients with Event (%)
Any AE	692 (37.6)	324 (36.2)	368 (38.9)

COVID-19 positive†	17 (1.8)	5 (1.1)	12 (2.4)
Symptomatic	9 (52.9)	2 (40.0)	7 (58.3)
General events			
Cerebral infarction	12 (0.7)	5 (0.6)	7 (0.7)
Hemorrhage intracranial	1 (0.1)	0 (0.0)	1 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.1)	1 (0.1)	0 (0.0)
Multiple organ dysfunction syndrome§	1 (0.1)	1 (0.1)	0 (0.0)
Infections			
Urinary tract infection	54 (2.9)	27 (3.0)	27 (2.9)
Pneumonia	27 (1.5)	10 (1.1)	17 (1.8)
Sepsis§	1 (0.1)	1 (0.1)	0 (0.0)
Systemic inflammatory response syndrome§	2 (0.1)	0 (0.0)	2 (0.2)

Neurological deficits			
Aphasia, motor	212 (11.5)	102 (11.4)	110 (11.7)
Aphasia, sensory	103 (5.6)	47 (5.3)	56 (5.9)
Hemiparesis, left	194 (10.5)	95 (10.6)	99 (10.5)
Hemiparesis, right	167 (9.1)	71 (7.9)	96 (10.2)
Neglect	99 (5.4)	48 (5.4)	51 (5.4)
Visual field disorders	103 (5.6)	49 (5.5)	54 (5.7)
Cognitive impairment	183 (10.0)	82 (9.2)	101 (10.7)
Persistent vegetative state	5 (0.3)	2 (0.2)	3 (0.3)
Seizure	10 (0.5)	4 (0.4)	6 (0.6)
Delirium	23 (1.3)	9 (1.0)	14 (1.5)
MedDRA coded AE ∫			
Blood and lymphatic system disorders	3 (0.2)	1 (0.1)	2 (0.2)
Cardiac disorders	31 (1.7)	16 (1.8)	15 (1.6)

Congenital, familial and genetic disorders	1 (0.1)	1 (0.1)	0 (0.0)
Endocrine disorders	1 (0.1)	1 (0.1)	0 (0.0)
Eye disorders	2 (0.1)	2 (0.2)	0 (0.0)
Gastrointestinal disorders	20 (1.1)	10 (1.1)	10 (1.1)
General disorders and administration site conditions	24 (1.3)	9 (1.0)	15 (1.6)
Hepatobiliary disorders	1 (0.1)	0 (0.0)	1 (0.1)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	14 (0.8)	9 (1.0)	5 (0.5)
Injury, poisoning and procedural complications	4 (0.2)	0 (0.0)	4 (0.4)
Investigations	4 (0.2)	3 (0.3)	1 (0.1)
Metabolism and nutrition disorders	9 (0.5)	4 (0.4)	5 (0.5)

Musculoskeletal and connective tissue disorders	15 (0.8)	5 (0.6)	10 (1.1)
Neoplasms – benign, malignant and unspecified (including cysts and polyps)	4 (0.2)	2 (0.2)	2 (0.2)
Nervous system disorders	45 (2.4)	28 (3.1)	17 (1.8)
Psychiatric disorders	18 (1.0)	8 (0.9)	10 (1.1)
Renal and urinary disorders	11 (0.6)	7 (0.8)	4 (0.4)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	14 (0.8)	10 (1.1)	4 (0.4)
Skin and subcutaneous tissue disorders	8 (0.4)	2 (0.2)	6 (0.6)
Surgical and medical procedures	2 (0.1)	1 (0.1)	1 (0.1)

Vascular disorders	27 (1.5)	12 (1.3)	15 (1.6)

† Up to final assessment at 90 ± 7 days.

¶ Assessed at 30 ± 3 days.

¶¶ Assessed at 90 ± 7 days and taking into consideration events between 30 and 90 days.

ϯ The denominator of this AE considers only patients included after February 2020. Symptomatic is a sub-item of COVID-19-positive and the percentage relates only to those with a positive test.

‡ The total number of SAEs in the Safety Population is 337 for an incidence rate of 59/1,000 person-months. In the early treatment group, the total number is 153 for an incidence rate of 56/1,000 person-months and 184 events with an incidence of 63/1,000 person-months for the late treatment group.

§ AEs that always qualified as SAEs.

∫ MedDRA coded by the Sponsor's team.

Table S4. Additional Details on Serious Adverse Events (SAEs).

Details of SAE	Total (N=337)	Early Treatment (N = 153)	Late Treatment (N = 184)
Intensity – no. (%)			
Mild	88 (26.1)	44 (28.8)	44 (23.9)
Moderate	114 (33.8)	41 (26.8)	73 (39.7)
Severe	135 (40.1)	68 (44.4)	67 (36.4)
Seriousness			
Life-threatening – no. (%)	67 (19.9)	25 (16.3)	42 (22.8)
Fatal – no. (%)	83 (24.6)	44 (28.8)	39 (21.2)
Resulted in disability/incapacity – no. (%)	49 (14.5)	19 (12.4)	30 (16.3)
Required or prolonged hospitalization – no. (%)	231 (68.5)	102 (66.7)	129 (70.1)
Hospitalization ongoing – no. (%)	6 (1.8)	2 (1.3)	4 (2.2)

Other – no. (%)	27 (8.0)	10 (6.5)	17 (9.2)
Causality assessment by the center: relationship with trial drug – no. (%)			
Not related	147 (43.6)	64 (41.8)	83 (45.1)
Unlikely	131 (38.9)	58 (37.9)	73 (39.7)
Possible	35 (10.4)	20 (13.1)	15 (8.2)
Probable	16 (4.7)	10 (6.5)	6 (3.3)
Certain	8 (2.4)	1 (0.7)	7 (3.8)
SAE sponsor assessment †			
Was the event expected? – no. (%)	60 (100.0)	25 (100.0)	35 (100.0)
Was the event classified as a SUSAR? – no. (%)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome – no. (%)			

Ongoing	66 (19.6)	29 (19.0)	37 (20.1)
Resolved	159 (47.2)	68 (44.4)	91 (49.5)
Resolved with sequelae	28 (8.3)	11 (7.2)	17 (9.2)
Death	84 (24.9)	45 (29.4)	39 (21.2)
Autopsy performed? – no. (%)			
no	70 (97.2)	40 (100.0)	30 (93.8)
yes	2 (2.8)	0 (0.0)	2 (6.3)
missing	12 (14.3)	5 (11.1)	7 (17.9)

† Sponsor assessment only for events defined as probable, possible or certain.

SUSAR, suspected unexpected serious adverse reaction.

Table S5. MedDRA coded Serious Adverse Events.

	Total (N=1940)	Early Treatment (N = 947)	Late Treatment (N = 993)
Event	No. of Patients with Event (%)	No. of Patients with Event (%)	No. of Patients with Event (%)
Any serious adverse event (SAE)	289 (14.9)	132 (13.9)	157 (15.8)
MedDRA coded adverse event (AE) †			
Blood and lymphatic system disorders	3 (0.2)	1 (0.1)	2 (0.2)
Cardiac disorders	51 (2.6)	20 (2.1)	31 (3.1)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	23 (1.2)	12 (1.3)	11 (1.1)

General disorders and administration site conditions	78 (4.0)	40 (4.2)	38 (3.8)
Hepatobiliary disorders	3 (0.2)	2 (0.2)	1 (0.1)
Immune system disorders	2 (0.1)	0 (0.0)	2 (0.2)
Infections and infestations	53 (2.7)	18 (1.9)	35 (3.5)
Injury, poisoning and procedural complications	15 (0.8)	4 (0.4)	11 (1.1)
Investigations	5 (0.3)	1 (0.1)	4 (0.4)
Metabolism and nutrition disorders	10 (0.5)	6 (0.6)	4 (0.4)
Musculoskeletal and connective tissue disorders	9 (0.5)	4 (0.4)	5 (0.5)
Neoplasms – benign, malignant and unspecified (including cysts and polyps)	17 (0.9)	13 (1.4)	4 (0.4)
Nervous system disorders	35 (1.8)	15 (1.6)	20 (2.0)

Psychiatric disorders	10 (0.5)	4 (0.4)	6 (0.6)
Renal and urinary disorders	18 (0.9)	8 (0.8)	10 (1.0)
Reproductive system and breast disorders	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	22 (1.1)	12 (1.3)	10 (1.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	9 (0.5)	3 (0.3)	6 (0.6)
Vascular disorders	69 (3.6)	29 (3.1)	40 (4.0)
† MedDRA coded by the Sponsor's team.			

Table S6. Additional Secondary Outcomes and Other Outcomes of Interest.

	Early Treatment (N=1006)		**Late Treatment (N=1007)**		**Adjusted Odds Ratio (95% CI)**
Outcome		**no. (%)**		**no. (%)**	
Outcomes at 30 ± 3 days					
modified Rankin scale (mRS) †	997	0: 250 (25.1) 1: 229 (23.0) 2: 145 (14.5) 3: 159 (15.9) 4: 129 (12.9) 5: 61 (6.1) 6: 24 (2.4)	1000	0: 215 (21.5) 1: 218 (21.8) 2: 193 (19.3) 3: 161 (16.1) 4: 133 (13.3) 5: 58 (5.8) 6: 22 (2.2)	0.93 (0.79 to 1.09)
Individual components of major extracranial bleeding	984		991		

Occurring in a critical part of the body		1 (0.1)		0 (0.0)	3.02 (0.16 to 437.70)
Decrease in hemoglobin of ≥2 g/dl over a 24-h period		1 (0.1)		2 (0.2)	0.61 (0.06 to 4.56)
Transfusion of ≥2 units of packed red blood cells		1 (0.1)		3 (0.3)	0.43 (0.04 to 2.61)
Outcomes at 90 ± 7 days					
mRS†	989	0: 272 (27.5) 1: 247 (25.0) 2: 140 (14.2) 3: 139 (14.1) 4: 103 (10.4) 5: 43 (4.3) 6: 45 (4.6)	994	0: 241 (24.2) 1: 243 (24.4) 2: 170 (17.1) 3: 170 (17.1) 4: 84 (8.5) 5: 37 (3.7) 6: 49 (4.9)	0.93 (0.79 to 1.09)

Favorable outcome (mRS ≤2)	989	659 (66.6)	965	654 (65.8)	1.03 (0.83 to 1.28)
Individual components of major extracranial bleeding	968		965		
Occurring in a critical part of the body		1 (0.1)		1 (0.1)	0.97 (0.08 to 11.93)
Decrease in hemoglobin of ≥2 g/dl over a 24-h period		1 (0.1)		3 (0.3)	0.42 (0.04 to 2.55)
Transfusion of ≥2 units of packed red blood cells		1 (0.1)		4 (0.4)	0.33 (0.03 to 1.76)
Myocardial infarction	968	3 (0.3)	965	1 (0.1)	2.36 (0.39 to 24.35)
Major cardiovascular events	968	41 (4.2)	965	55 (5.7)	0.73 (0.48 to 1.11)
Transient ischemic stroke	968	5 (0.5)	965	6 (0.6)	0.84 (0.26 to 2.66)

Undetermined stroke	968	3 (0.3)	965	1 (0.1)	2.58 (0.42 to 26.91)
† Analyzed using ordinal logistic regression.					

Table S7. Sensitivity Analysis of Primary Outcome.

	Early Treatment (N = 1006)		Late Treatment (N = 1007)		Measure of Effect	Unadjusted Effect (95% CI)
Outcome						
		no. (%)		no. (%)		
Primary outcome	984	29 (2.9)	991	41 (4.1)		
Zelig comparison†					Odds ratio	0.70 (0.43 to 1.15)
Without multiple imputation‡					Odds ratio	0.71 (0.43 to 1.15)
Unadjusted difference¶					Risk difference	−1.19 (−2.88 to 0.45)

† Penalized logistic regression with stratification factors as covariates (age, NIHSS, infarct size)

‡ Penalized logistic regression using Firth's method with stratification factors as covariate

¶ Unadjusted risk difference with 95% CI calculated using the Miettinen-Nurminen method.

Table S8. Time-to-event Analysis.

	Early Treatment (N = 1006)	Late Treatment (N = 1007)	Risk Difference (95% CI)*	Odds Ratio (95%)*	Adjusted Hazard Ratio effect (95% CI)†
At 30 days‡					
Primary outcome	29 (2.9%)	41 (4.1%)	-1.19 (-2.79 to 0.42)	0.70 (0.43 to 1.14)	0.72 (0.45 to 1.15)
Major extracranial bleeding	3 (0.3%)	5 (0.5%)	-0.20 (-0.75 to 0.35)	0.60 (0.14 to 2.52)	0.72 (0.17 to 2.99)
Symptomatic intracranial hemorrhage	2 (0.2%)	2 (0.2%)	0.00 (-0.39 to 0.39)	1.00 (0.14 to 7.13)	1.01 (0.14 to 7.15)
Recurrent ischemic stroke	14 (1.4%)	25 (2.5%)	-1.09 (-2.30 to 0.11)	0.55 (0.29 to 1.07)	0.59 (0.31 to 1.14)
Systemic embolism	4 (0.4%)	9 (0.9%)	-0.50 (-1.20 to 0.21)	0.44 (0.14 to 1.45)	0.55 (0.17 to 1.79)
Vascular death	11 (1.1%)	10 (1.0%)	0.10 (-0.79 to 0.99)	1.10 (0.47 to 2.61)	1.09 (0.46 to 2.58)
At 90 days‡					
Composite outcome	36 (3.6%)	54 (5.5%)	-1.86 (-3.70 to -0.03)	0.65 (0.42 to 1.00)	0.67 (0.44 to 1.02)
Major extracranial bleeding	3 (0.3%)	8 (0.8%)	-0.50 (-1.15 to 0.15)	0.37 (0.10 to 1.41)	0.50 (0.13 to 1.90)

Symptomatic intracranial hemorrhage	2 (0.2%)	2 (0.2%)	0.00 (-0.39 to 0.39)	1.00 (0.14 to 7.13)	1.01 (0.14 to 7.15)
Recurrent ischemic stroke	18 (1.8%)	30 (3.1%)	-1.27 (-2.63 to 0.10)	0.58 (0.32 to 1.05)	0.62 (0.35 to 1.12)
Systemic embolism	4 (0.4%)	10 (1.0%)	-0.60 (-1.33 to 0.13)	0.40 (0.12 to 1.28)	0.51 (0.16 to 1.61)
Vascular death	17 (1.7%)	16 (1.6%)	0.10 (-1.01 to 1.22)	1.07 (0.54 to 2.12)	1.06 (0.54 to 2.10)

‡ All events that happened within 30 and 90 days, respectively.

† Model estimated using penalized survival model with adjustment for stratification variables (age, NIHSS and infarct size).

* Primary and binary secondary outcomes analyzed using survival methods. Risk difference and odds ratio at 30 and 90 days were calculated from the non-parametric Aalen-Johansen estimator taking competing risk (death without prior event) into account. Hazard ratios calculated from an adjusted cause-specific penalized survival model.

Table S9. Results of Per-Protocol Analyses.

	Early Treatment (N = 887)		Late Treatment (N = 903)		Measure of Effect	Adjusted Effect (95% CI)†
Outcome	N‡		N‡			
		no. (%)		no. (%)		
Primary outcome	870	28 (3.2)	891	37 (4.2)	Odds ratio	0.81 (0.49 to 1.34)
					Risk difference	-0.88 (-2.68 to 0.91)
Secondary outcomes at 30 days						
Major extracranial bleeding	870	3 (0.3)	891	4 (0.4)	Odds ratio	0.80 (0.18 to 3.28)

Symptomatic intracranial hemorrhage	870	2 (0.2)	891	2 (0.2)	Odds ratio	1.03 (0.16 to 6.65)
Recurrent ischemic stroke	870	14 (1.6)	891	23 (2.6)	Odds ratio	0.63 (0.32 to 1.21)
Systemic embolism	870	3 (0.3)	891	8 (0.9)	Odds ratio	0.43 (0.11 to 1.41)
Vascular death	870	10 (1.1)	891	9 (1.0)	Odds ratio	1.16 (0.47 to 2.88)
Non-major bleeding	870	23 (2.6)	891	20 (2.2)	Odds ratio	1.20 (0.66 to 2.22)
Modified Rankin scale (mRS)	879	0: 229 (26.1) 1: 199 (22.6) 2: 138 (15.7) 3: 135 (15.4) 4: 113 (12.9)	898	0: 198 (22.0) 1: 199 (22.2) 2: 173 (19.3) 3: 143 (15.9) 4: 119 (13.3)	Odds ratio	0.90 (0.76 to 1.06)

		5: 46 (5.2) 6: 19 (2.2)		5: 48 (5.3) 6: 18 (2.0)		
Secondary outcomes at 90 days						
Major extracranial bleeding	855	3 (0.4)	870	7 (0.8)	Odds ratio	0.47 (0.11 to 1.60)
Symptomatic intracranial hemorrhage	855	2 (0.2)	870	2 (0.2)	Odds ratio	1.01 (0.16 to 6.53)
Recurrent ischemic stroke	855	17 (2.0)	870	27 (3.1)	Odds ratio	0.65 (0.35 to 1.17)
Systemic embolism	855	3 (0.4)	870	9 (1.0)	Odds ratio	0.38 (0.09 to 1.19)

Vascular death	855	15 (1.8)	870	14 (1.6)	Odds ratio	1.10 (0.53 to 2.30)
All-cause mortality	876	38 (4.3)	870	37 (4.1)	Odds ratio	1.04 (0.65 to 1.66)
Non-major bleeding	855	32 (3.7)	870	32 (3.7)	Odds ratio	1.03 (0.62 to 1.70)
mRS	872	0: 247(28.3) 1: 224 (25.7) 2: 122 (14.0) 3: 122 (14.0) 4: 84 (9.6) 5: 35 (4.0) 6: 38 (4.4)	892	0: 223 (25.0) 1: 216 (24.2) 2: 160 (17.9) 3: 147 (16.5) 4: 76 (8.5) 5: 32 (3.6) 6: 38 (4.3)	Odds ratio	0.91 (0.77 to 1.08)
Favorable outcome (mRS≤2)	872	593 (68.0)	892	599 (67.2)	Odds ratio	1.01 (0.81 to 1.28)

† The analyses were stratified or adjusted using randomization strata.

‡ Numbers of imputed values are 17 and 12 for early and late treatment, respectively.

Table S10. Protocol Deviations.

	Total (N=2013)	Early Treatment (N = 1006)	Late Treatment (N = 1007)
Violation of inclusion or exclusion criteria	41 (2.0%)	22 (2.2%)	19 (1.9%)
Participant received wrong treatment	6 (0.3%)	3 (0.3%)	3 (0.3%)
Randomization outside the correct window	48 (2.4%)	17 (1.7%)	31 (3.1%)
Crossover †	66 (3.3%)	41 (4.1%)	25 (2.5%)
Treatment did not start †	10 (0.5%)	6 (0.6%)	4 (0.4%)
Treatment started too late (>336h) †	13 (0.6%)	5 (0.5%)	8 (0.8%)
Visit 7 in the correct time window‡	5 (0.2%)	0 (0.0%)	5 (0.5%)
Visit 8 in the correct time window‡	56 (2.8%)	36 (3.6%)	20 (2.0%)
Patient included in the PPS	1790 (88.9%)	887 (88.2%)	903 (89.7%)

† If treatment delay (causing either crossover, start after over 336 h, or not started at all) was caused by an event the patient was not considered as deviating from the protocol.

‡ The exclusion for violating the time window was considered if the visit at 30 days after randomization was done too early and no later visit was made, and for visit 8 if the visit took place earlier than 83 days after randomization.

Table S11. Additional Results of Subgroup Analysis.

	Early Treatment (N = 1006)		Late Treatment (N = 1007)		Odds Ratio (95% CI)†
Subgroup – Country	N_S		N_S		
Austria	48	1 (2.1)	49	2 (4.1)	0.60 (0.05 to 4.68)
Belgium	89	1 (1.1)	94	2 (2.1)	0.63 (0.06 to 4.81)
Finland	40	0 (0.0)	42	1 (2.4)	Not estimable
Germany	95	2 (2.1)	94	2 (2.1)	0.99 (0.15 to 6.53)
Greece	9	1 (11.1)	10	0 (0.0)	Not estimable
India	25	3 (12.0)	28	0 (0.0)	Not estimable
Ireland	8	0 (0.0)	9	0 (0.0)	Not estimable
Israel	16	1 (6.3)	14	1 (7.1)	0.87 (0.06 to 11.70)
Italy	9	0 (0.0)	12	0 (0.0)	Not estimable
Japan	99	3 (3.0)	93	10 (10.8)	0.29 (0.07 to 0.92)
Norway	41	0 (0.0)	38	1 (2.6)	Not estimable

Portugal	14	0 (0.0)	14	1 (7.1)	Not estimable
Slovakia	7	2 (28.6)	8	1 (12.5)	2.27 (0.23 to 30.51)
Switzerland	247	7 (2.8)	248	9 (3.6)	0.79 (0.29 to 2.08)
United Kingdom	237	8 (3.4)	238	11 (4.6)	0.73 (0.29 to 1.80)

† Odds ratio calculated for the composite primary outcome in each subgroup without adjustment for the other stratification factors.

N_s is the number of patients in each country and in each treatment group.

Table S12. Representativeness of Study Participants.

Category	
Disease, problem or condition under investigation	Ischemic stroke associated with atrial fibrillation (AF)
Special considerations related to	
Sex and gender	AF is common in men and women but women have a higher risk of AF-associated complications such as stroke.[1] Women are also less likely to be anticoagulated when they have AF and are typically underrepresented in anticoagulation trials.[2]
Age	AF is more common in older people, as is risk of bleeding complications with anticoagulants.
Race and ethnic group	AF is under-detected in African American people[3] compared to Caucasian and Asian Americans. In addition, black individuals are less likely to be anticoagulated after a new diagnosis of AF,[4] or to receive a DOAC after AF-associated ischemic stroke.[5] Anticoagulant-associated bleeding is more common in Asian people, although DOACs appear to be safer in Asian people.[6]
Geography	Rates of AF-related complications and anticoagulation-associated bleeding vary by region, with the highest morbidity rates in non-Asian countries and lowest uptakes of

	anticoagulants in Asian[7] and non-European countries.
Other considerations	
Overall representativeness of the trial	Participants in this trial were recruited from European and Asian countries and from Israel – 86.0% were enrolled from Europe. Women were well represented and accounted for 45% of randomized participants. Older people were well represented. The median age of participants was 77 years and ¼ were aged over 84 years. People with major stroke made up 23% of randomized participants. 53% underwent CT imaging as their initial brain imaging.

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. Circulation. 2022;145:e153-e639.
2. Yong CM, Tremmel JA, Lansberg MG, et al. Sex differences in oral anticoagulation and outcomes of stroke and intracranial bleeding in newly diagnosed atrial fibrillation. J Am Heart Assoc. 2020;9:e015689. doi: 10.1161/JAHA.120.015689. Epub 2020 May 12. PMID: 32394763; PMCID: PMC7660841.
3. Heckbert SR, Austin TR, Jensen PN, et al. Differences by race/ethnicity in the prevalence of clinically detected and monitor-detected atrial fibrillation: MESA. Circ Arrhythm Electrophysiol. 2020;13:e007698. doi: 10.1161/CIRCEP.119.007698. Epub 2020 Jan 14. PMID: 31934795; PMCID: PMC7204495.
4. Essien UR, Magnani JW, Chen N, et al. Race/ethnicity and sex-related differences in direct oral anticoagulant initiation in newly diagnosed atrial fibrillation: A retrospective study of Medicare data. J Natl Med Assoc. 2020;112:103-108. doi: 10.1016/j.jnma.2019.10.003. Epub 2020 Feb 6. PMID: 32035755; PMCID: PMC7183759.
5. Sur NB, Wang K, Di Tullio MR, et al. Disparities and temporal trends in the use of anticoagulation in patients with ischemic stroke and atrial fibrillation. Stroke. 2019;50(6):1452-1459. doi: 10.1161/STROKEAHA.118.023959. Epub 2019 May 14. PMID: 31084325; PMCID: PMC6538423.
6. Wang KL, Lip GY, Lin SJ, et al. Non-vitamin k antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: Meta-analysis. Stroke. 2015 Sep;46(9):2555-61. doi: 10.1161/STROKEAHA.115.009947. Epub 2015 Jul 30. PMID: 26304863; PMCID: PMC4542566.
7. Fox KAA, Virdone S, Bassand JP, et al.. Do baseline characteristics and treatments account for geographical disparities in the outcomes of patients with newly diagnosed atrial fibrillation? The prospective GARFIELD-AF registry. BMJ Open. 2022;12:e049933. doi: 10.1136/bmjopen-2021-049933. PMID: 34996784; PMCID: PMC8744109.

Table S13. Stroke Size Classification.

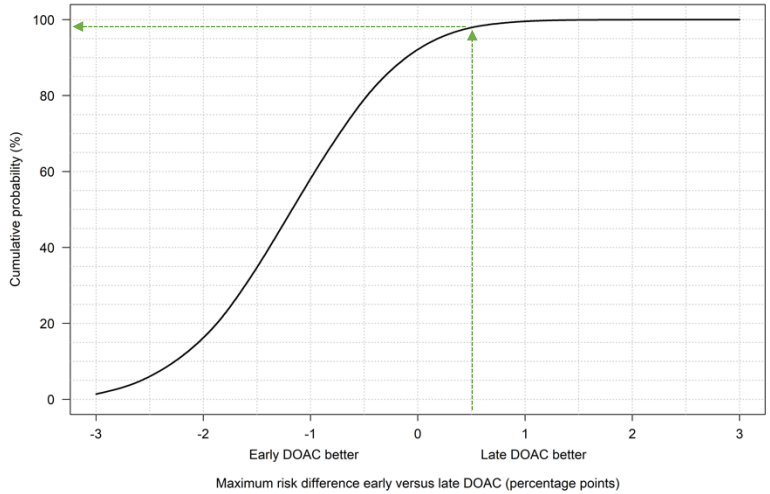
Minor	Moderate	Major
Lesion is ≤ 1.5 cm in anterior or posterior circulation	Lesion is in a cortical superficial branch of the middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of the posterior cerebral artery, or in a cortical superficial branch of the anterior cerebral artery	Anterior: lesion involves the whole territory of the MCA, posterior cerebral artery, or anterior cerebral artery, in two cortical superficial branches of MCA, in a cortical superficial branch of the MCA associated with the MCA deep branch, or in > 1 artery territory (e.g., MCA associated with anterior cerebral artery territories) Posterior: lesion is ≥ 1.5 cm in the brainstem or cerebellum
Caveat: multiple minor tiny spots (embolic shower) = minor stroke	Caveat: two minor lesions = moderate lesion (the sum of the lesions)	Caveat: two moderate lesions = large lesion

Ischemic stroke size classification is based on recent guidelines.[4]

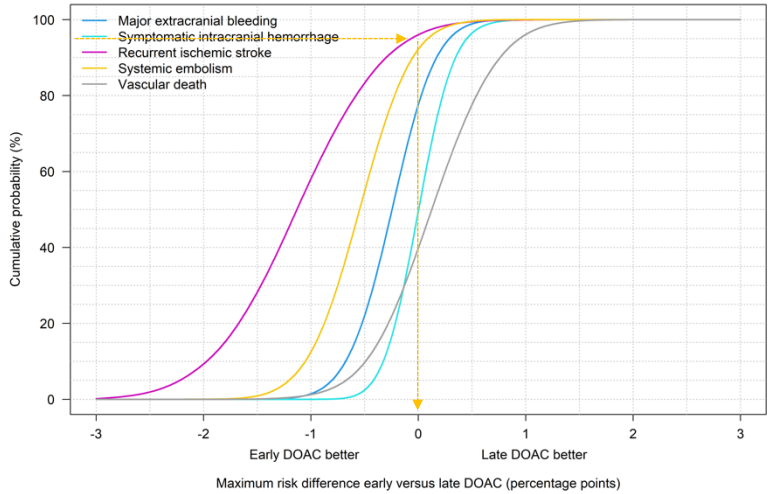
Supplemental Figures

Figure S1 Cumulative Probabilities of Risk Difference of the Composite Outcome (A) and its Components (B) between Early versus Late DOAC Initiation

A



B

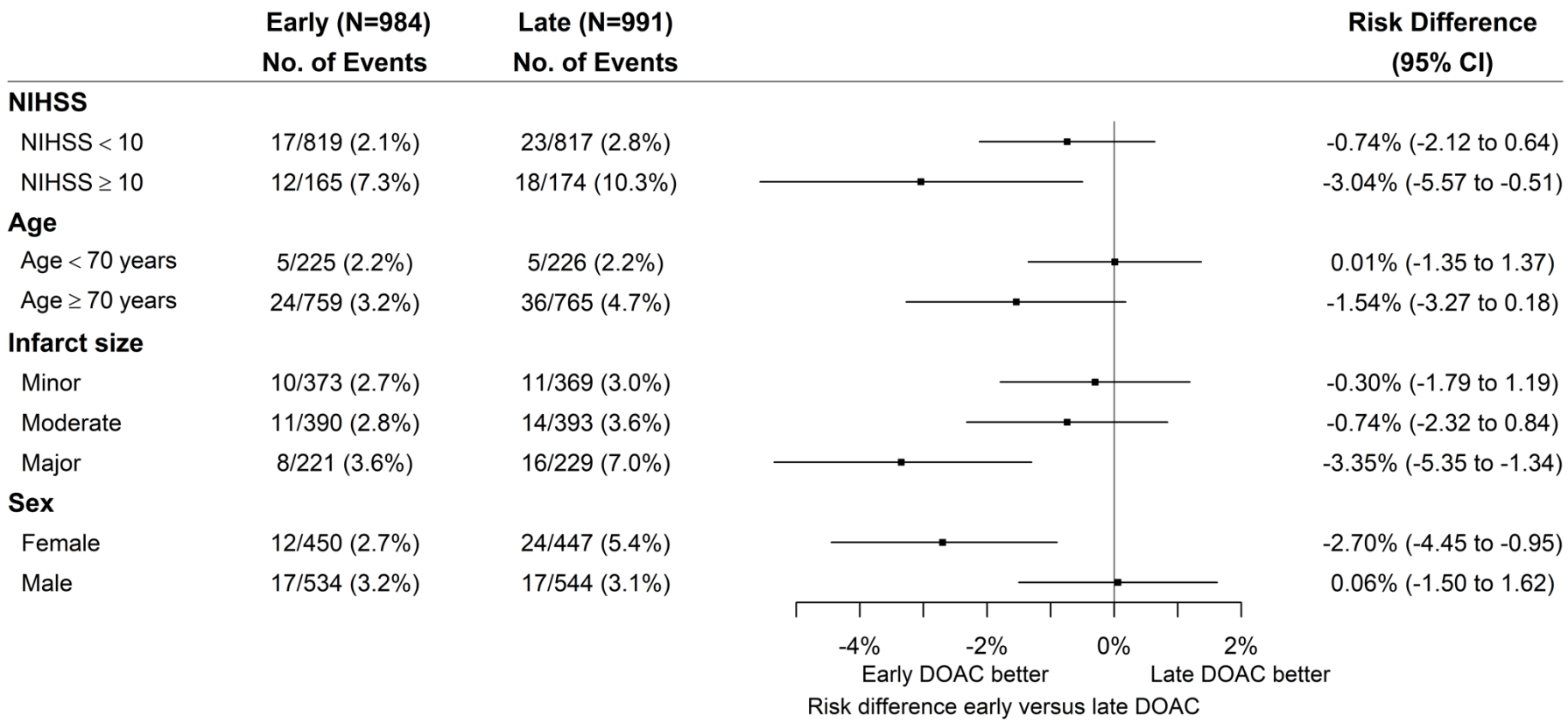


DOAC, direct oral anticoagulant

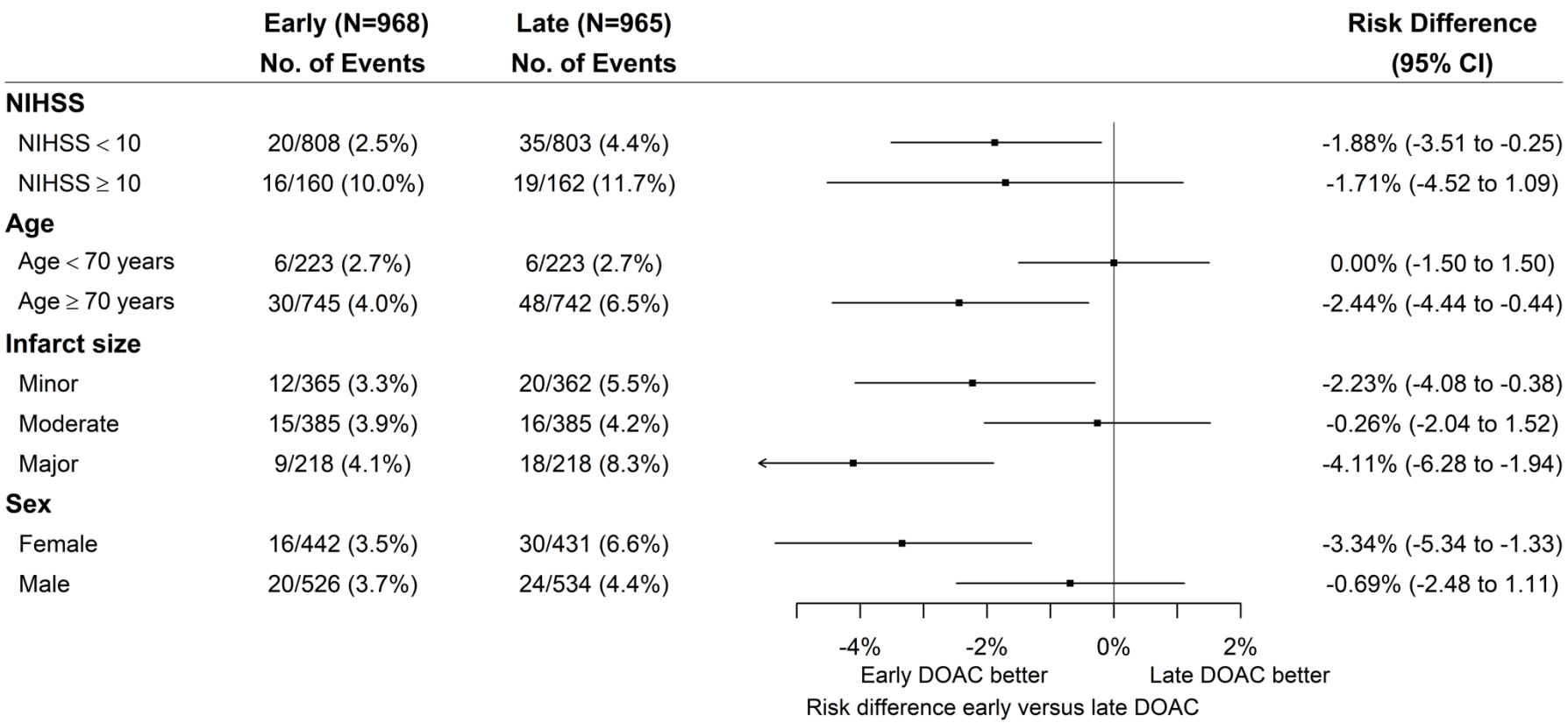
Probability (vertical axis) of having a risk difference equal to or smaller than a specific value (horizontal axis). For example, panel A, there is a 98% probability that early DOAC will increase the risk of the primary composite outcome by not more than 0.5% (green arrows). The purple curve, panel B, indicates a 95% probability that there is no increase in risk of recurrent ischemic stroke (risk difference of 0%) with early treatment (yellow arrow).

Figure S2. Subgroup Analyses of the Composite Outcome at 30 (A) and 90 (B) Days.

A

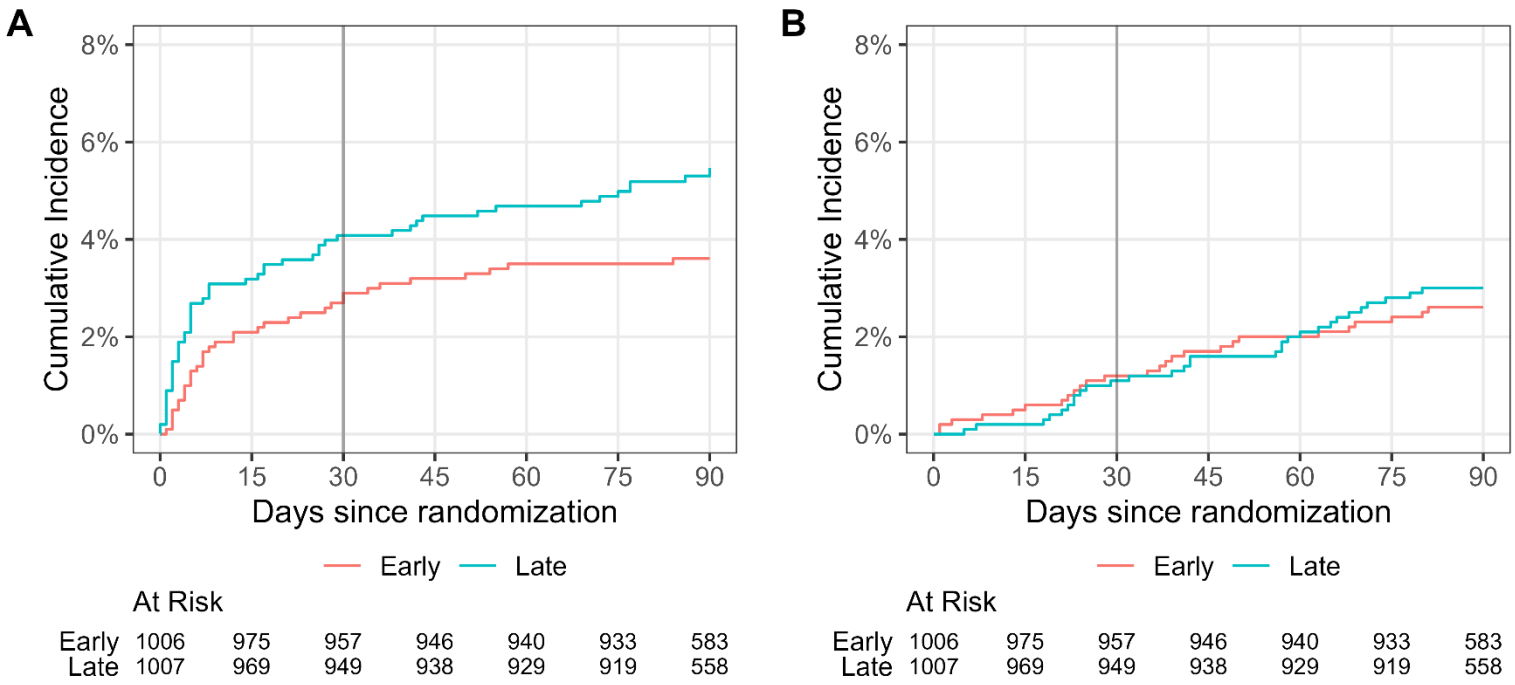


B



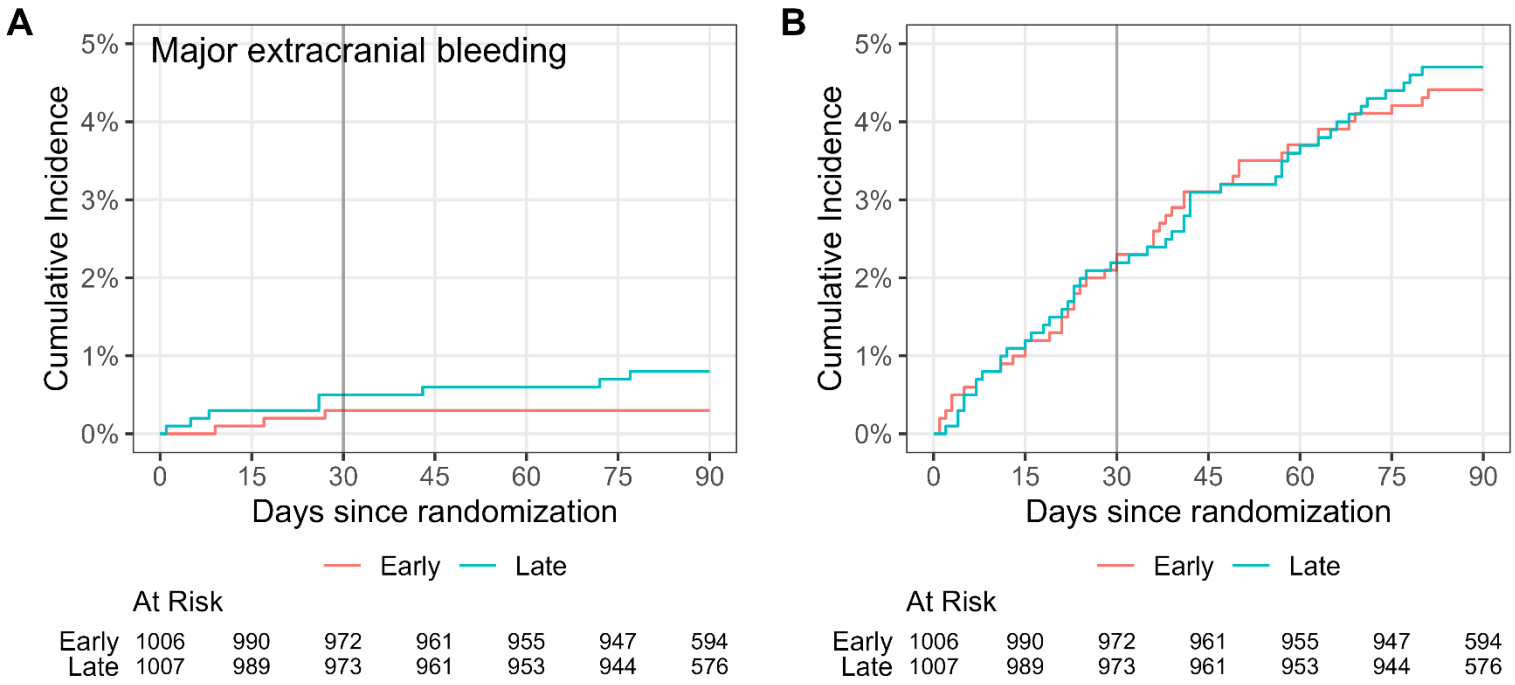
Point estimates (squares) and two-sided 95% confidence intervals (bars) for the treatment effect defined as risk difference (early − late DOAC) for each subgroup are shown.

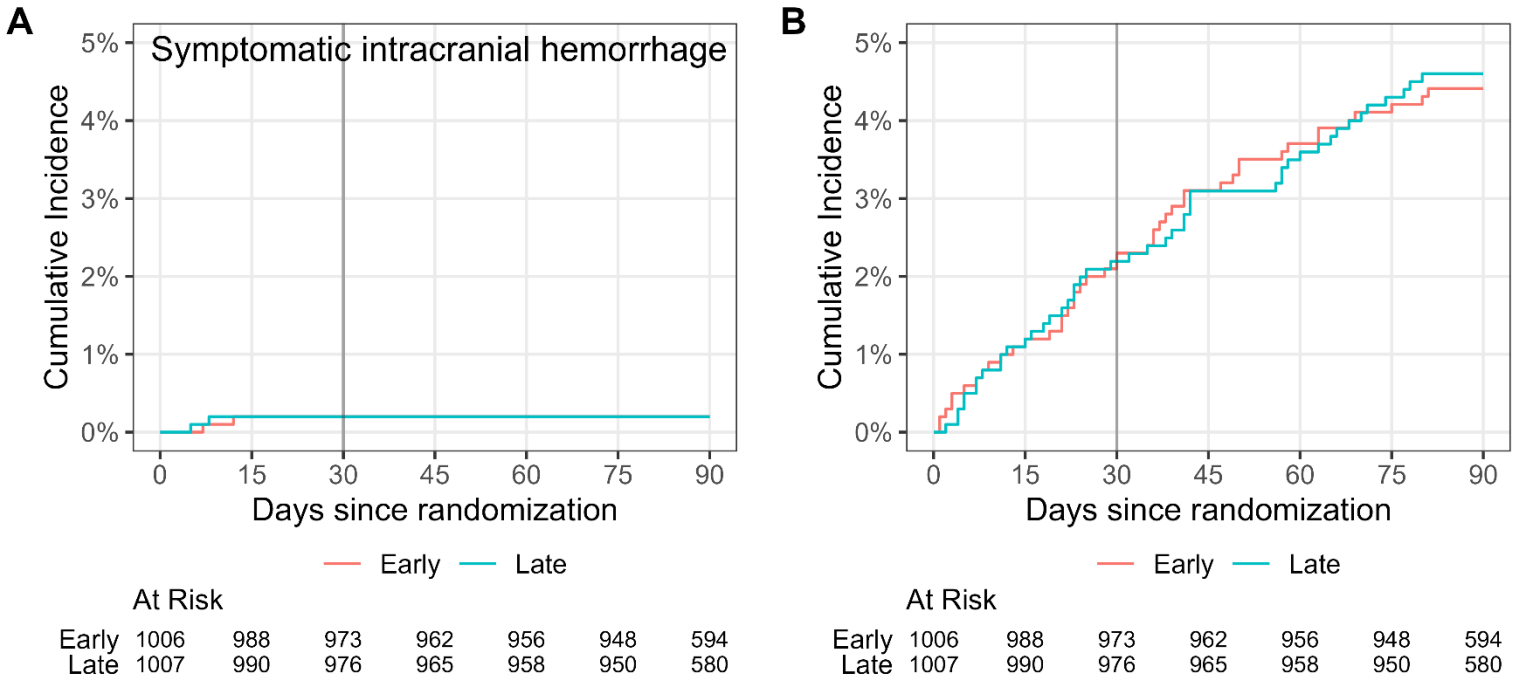
Figure S3. Cumulative Incidence Plot of the Primary Outcome.

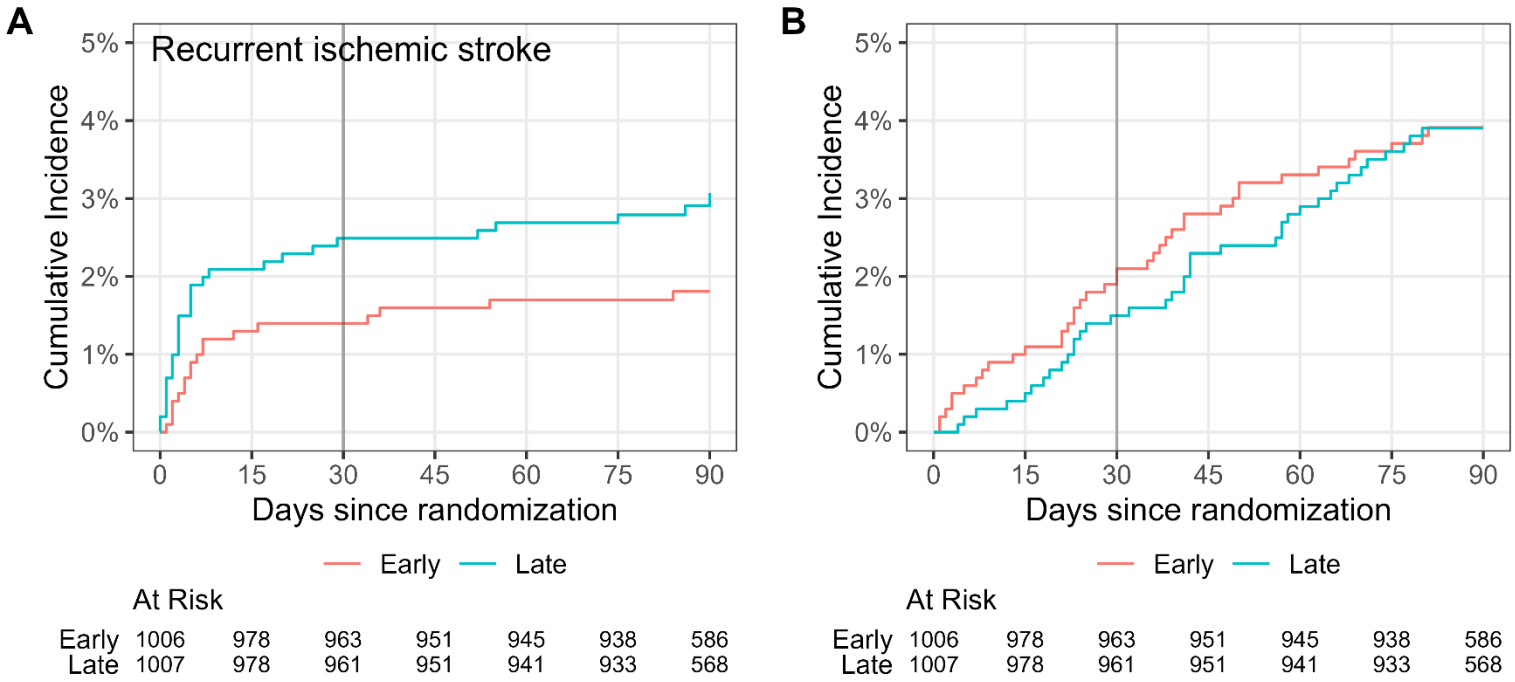


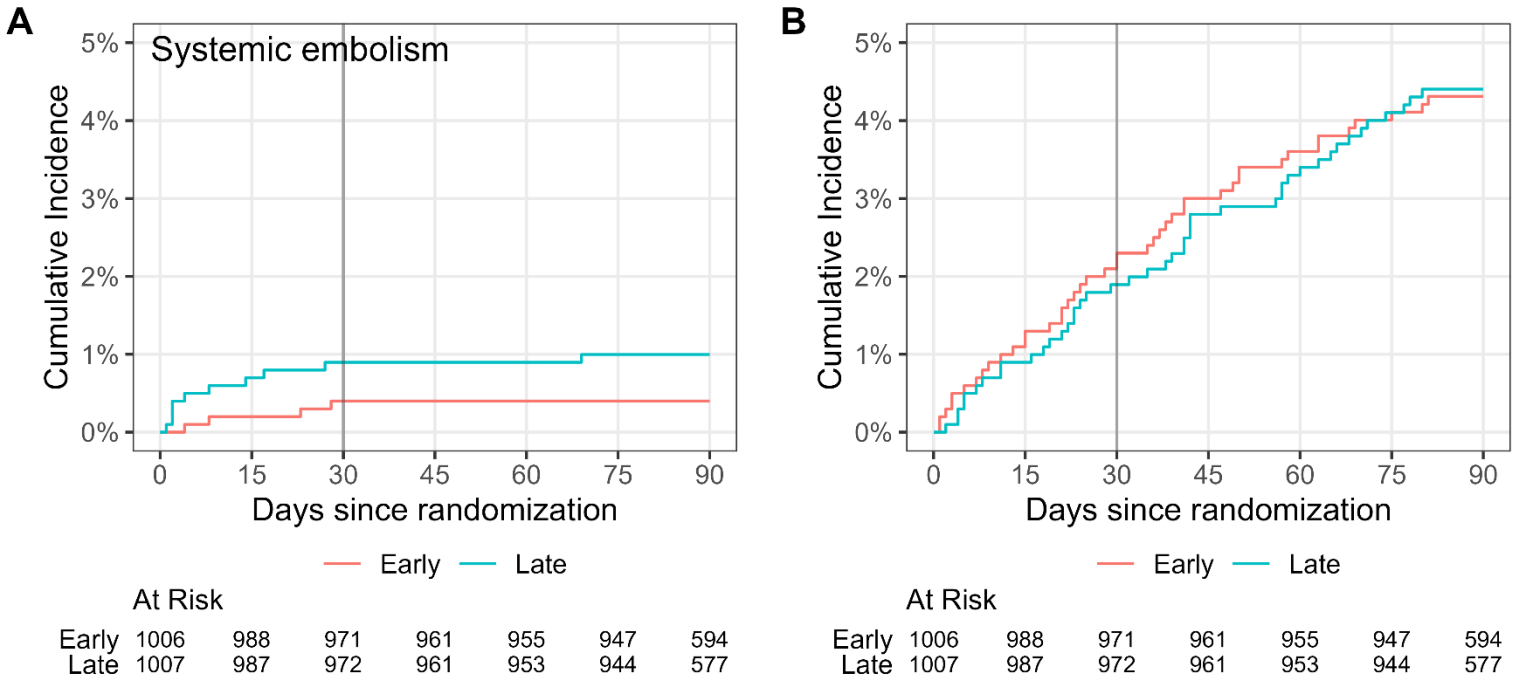
Cumulative incidences of A) the primary outcome and B) the competing event (death without previous primary outcome) using the non-parametric Aalen-Johansen estimator.

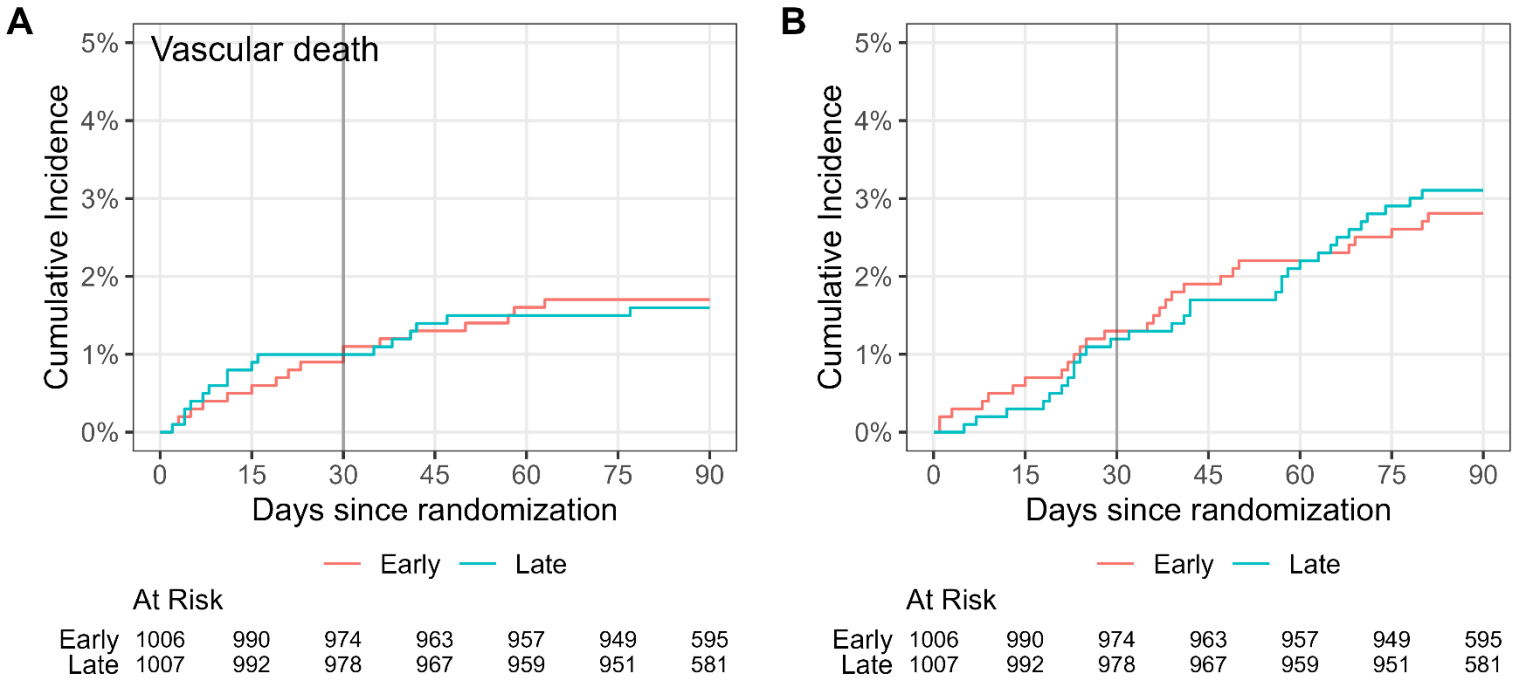
Figure S4. Cumulative Incidence Plots of Individual Components of the Composite Outcome.




A
Symptomatic intracranial hemorrhage
Cumulative Incidence
5%
4%
3%
2%
1%
0%
0
15
30
45
60
75
90
Days since randomization
Early
Late
At Risk
Early 1006 988 973 962 956 948 594
Late 1007 990 976 965 958 950 580
B
Cumulative Incidence
5%
4%
3%
2%
1%
0%
0
15
30
45
60
75
90
Days since randomization
Early
Late
At Risk
Early 1006 988 973 962 956 948 594
Late 1007 990 976 965 958 950 580

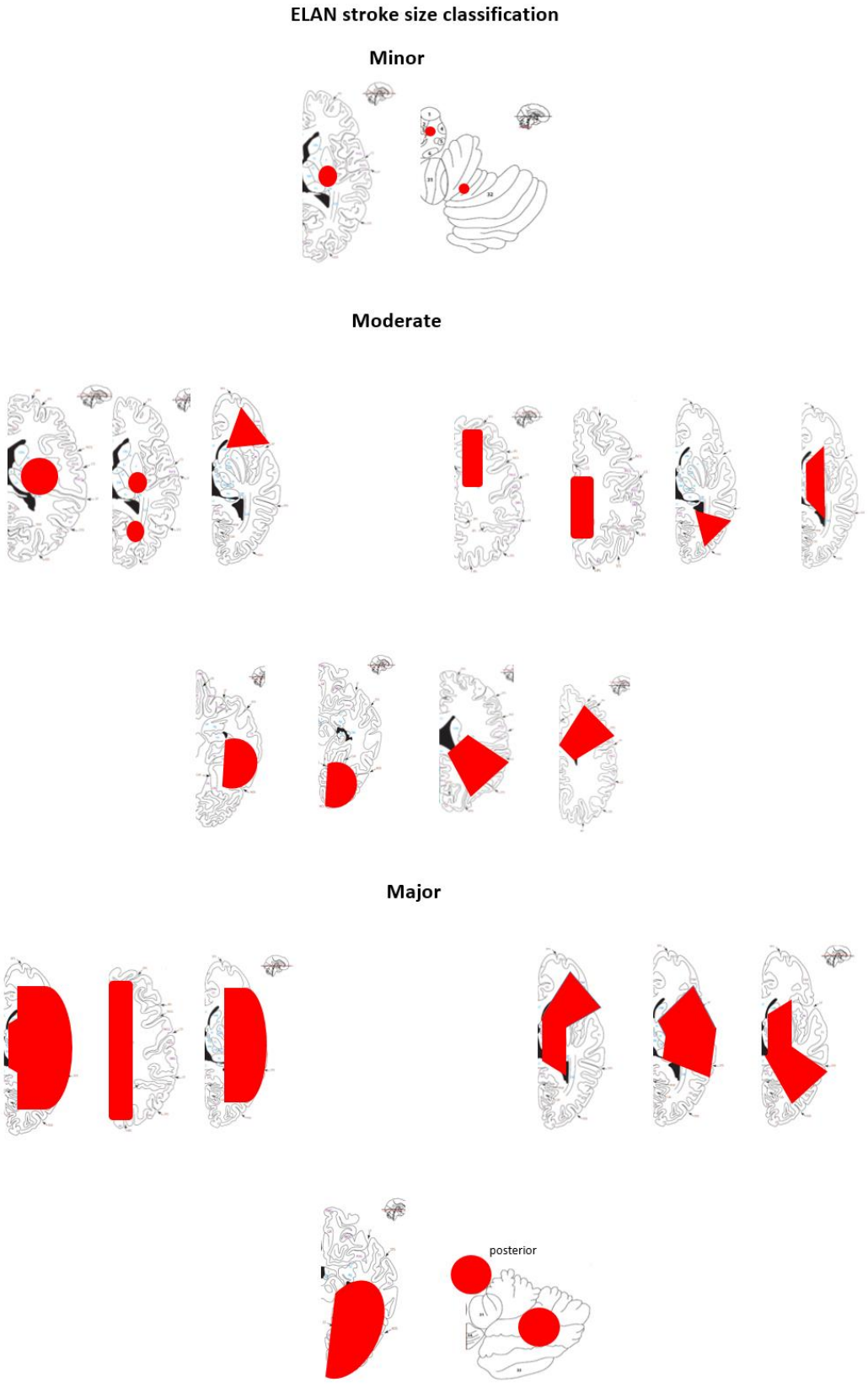

A
Recurrent ischemic stroke
Cumulative Incidence
5%
4%
3%
2%
1%
0%
0
15
30
45
60
75
90
Days since randomization
Early
Late
At Risk
Early 1006 978 963 951 945 938 586
Late 1007 978 961 951 941 933 568
B
Cumulative Incidence
5%
4%
3%
2%
1%
0%
0
15
30
45
60
75
90
Days since randomization
Early
Late
At Risk
Early 1006 978 963 951 945 938 586
Late 1007 978 961 951 941 933 568


A
Systemic embolism
Cumulative Incidence
5%
4%
3%
2%
1%
0%
0
15
30
45
60
75
90
Days since randomization
Early
Late
At Risk
Early 1006 988 971 961 955 947 594
Late 1007 987 972 961 953 944 577
B
Cumulative Incidence
5%
4%
3%
2%
1%
0%
0
15
30
45
60
75
90
Days since randomization
Early
Late
At Risk
Early 1006 988 971 961 955 947 594
Late 1007 987 972 961 953 944 577



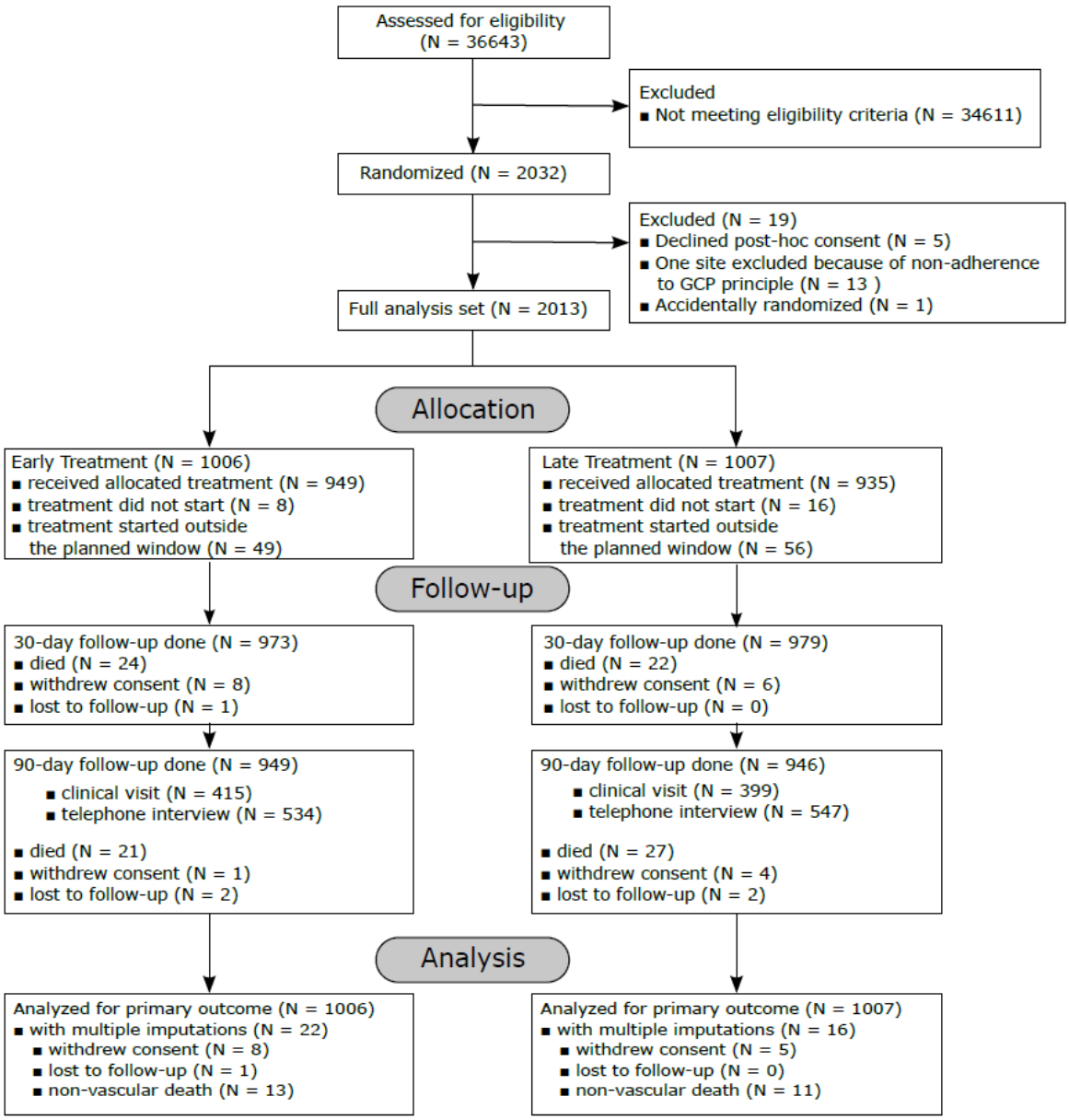
Cumulative incidences of A) the individual component of the primary outcome and B) the competing event (death without previous primary outcome) using the non-parametric Aalen-Johansen estimator.

Figure S5. Stroke Size Classification.



For further information please see also Table S13.

Figure S6. Complete Flowchart.



One participant had an event within 30 days and later withdrew consent without attending the 30-day follow-up appointment. One participant who died within 30 days, had previously had an event adjudicated as primary outcome.

Clinical Event Committee: Event Adjudication Forms

<u>Major Bleeding</u>: Event Adjudication Form

Patient ID: 0679 - _ _ _ - _ _ _
Event no. _ _ _
Patient YOB: _ _ _ _ (yyyy)
Site diagnosis: _____
Event date: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Adjudicators:

☐ CEC Members
1. Full name _____
2. Full name _____

☐ CEC Chair Full name _____

Date of adjudication: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Major bleeding: Study definition

Major bleeding (major bleeds are those that result in death or are life-threatening) is defined as clinically overt bleeding that is accompanied by one or more of the following:

- Decrease in haemoglobin of ≥ 2g / dl over a 24-hour period
- Transfusion of ≥ 2 units of packed red blood cells
- Occurring in a critical part of the body (symptomatic intracranial (sICH), intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal)

  A relevant symptomatic intracranial haemorrhage, this includes subdural, epidural, subarachnoidal and intracerebral haemorrhage, is defined as haemorrhage that leads to a clinical worsening and hospitalisation and is assessed by the treating physician to be likely the cause of the new neurological symptom or the death. Intracerebral haemorrhage due to a trauma will not be considered.

  For all other organs: in order for bleeding (e.g. gastrointestinal) in a critical area or organ to be classified as a major bleeding it must be associated with a symptomatic clinical presentation.

Section I: Final classification

Criteria for Major Bleeding

Please note: at least one of the following criteria must be YES to adjudicate this event as "major bleeding".

	YES	NO/UNCERTAIN
Fatal	☐	☐
Life-threatening	☐	☐

Please note: at least one of the following criteria must be YES to adjudicate this event as "major bleeding".

	YES	NO/UNCERTAIN
Decrease in the haemoglobin level of ≥ 2g/dL over a 24-hour period	☐	☐
Transfusion of ≥ 2 or more units of packed red blood cells	☐	☐
Occurring in a critical part of the body (symptomatic intracranial (siCH), intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal)	☐	☐
All other organs **and** associated with a symptomatic clinical presentation	☐	☐

Relevant symptomatic intracranial haemorrhage (including subdural, epidural, subarachnoidal and intracerebral haemorrhage)

Please note: at least one of the following criteria must be YES to adjudicate this event as "symptomatic intracranial haemorrhage". Intracranial haemorrhages due to a trauma will not be considered.

	YES	NO/UNCERTAIN
Leads to a clinical worsening and hospitalisation	☐	☐
Is assessed by the treating physician to be likely the cause of the new neurological symptom or death	☐	☐

Section II: Adjudication Decision
(Based on review of source documents)

Please check ONE only:

Event is adjudicated as major haemorrhage	☐
Event is adjudicated as relevant symptomatic intracranial haemorrhage	☐
Event CANNOT be adjudicated as major haemorrhage	☐
Event CANNOT be adjudicated as relevant symptomatic intracranial haemorrhage	☐
Event is NOT adjudicated: More documentation is needed	☐ → Please describe the documentation required in the space below
Event is NOT adjudicated: CEC Members could not reach an agreement	☐ → The event will be adjudicated by the CEC Chair

Documentation required:

Section III: Comments

Please use the following space for any comments or remarks.

Adjudicator(s) signature

CEC Members

Please note: both CEC members are required to sign the form.

1. _____

2. _____

Place and date

_____

CEC Chair

(Please leave this section blank if the event has been adjudicated by the CEC Members.)

Place and date

<u>Recurrent Ischaemic stroke</u>: Event Adjudication Form

Patient ID: 0679 - _ _ _ - _ _ _
Event no. _ _ _
Patient YOB: _ _ _ _ (yyyy)
Site diagnosis: _____
Event date: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Adjudicators:

☐ CEC Members

1. Full name _____
2. Full name _____

☐ CEC Chair Full name _____

Date of adjudication: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Recurrent ischaemic stroke: Study definition

A recurrent ischaemic stroke is defined as:

- New sudden focal neurological deficit of presumed cerebrovascular aetiology, occurring > 24 hours after the index ischaemic stroke, that persisted beyond 24 hours and was not due to another identifiable cause (transient ischaemic attack - TIA), defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischaemia without cerebral infarction on imaging, is not judged as stroke) and/or
- by brain imaging (CT or MRI).

Section I: Final classification

Criteria for Recurrent Ischaemic Stroke

Please note: at least one of the following criteria must be YES to adjudicate this event as "recurrent ischaemic stroke".

	YES	NO/UNCERTAIN
Diagnosed by CT scan	☐	☐
Diagnosed by MRI scan	☐	☐
Diagnosed using a time based definition	☐	☐

(New sudden focal neurological deficit of presumed cerebrovascular aetiology, occurring > 24 hours after the index ischaemic stroke, that persisted beyond 24 hours and was not due to another identifiable cause (transient ischaemic attack - TIA), defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischaemia without cerebral infarction on imaging, is not judged as stroke).

Section II: Adjudication Decision

(Based on review of source documents)

Please check ONE only:

Event is adjudicated as recurrent ischaemic stroke	☐
Event CANNOT be adjudicated as recurrent ischaemic stroke	☐
Event is NOT adjudicated: More documentation is needed	☐ → Please describe the documentation required in the space below
Event is NOT adjudicated: CEC Members could not reach an agreement	☐ → The event will be adjudicated by the CEC Chair

Documentation required:

Section III: Comments

Please use the following space for any comments or remarks.

Adjudicator(s) signature

CEC Members

Please note: both CEC members are required to sign the form.

1. _____

2. _____

Place and date

_____

CEC Chair

(Please leave this section blank if the event has been adjudicated by the CEC Members.)

_____

Place and date

_____

<u>Systemic Embolism</u>: Event Adjudication Form

Patient ID: 0679 - _ _ _ - _ _ _
Event no. _ _ _
Patient YOB: _ _ _ _ (yyyy)
Site diagnosis: _____
Event date: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Adjudicators:

☐ CEC Members
1. Full name _____
2. Full name _____

☐ CEC Chair Full name _____

Date of adjudication: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Systemic Embolism: Study definition

Systemic embolism is defined as:

- Abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion of an extremity or organ other than the brain in absence of another likely mechanism (e.g. atherosclerosis, instrumentation or trauma).

Section I: Final Classification

Criteria for Systemic Embolism

Please note: the following criterion must be YES to adjudicate this event as “systemic embolism”.

	YES	NO/UNCERTAIN
Abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion of an extremity or organ other than the brain in absence of another likely mechanism (e.g. atherosclerosis, instrumentation or trauma).	☐	☐

Section II: Adjudication Decision

(Based on review of source documents)

Please check ONE only:

Event is adjudicated as systemic embolism	☐
Event CANNOT be adjudicated as systemic embolism	☐
Event is NOT adjudicated: More documentation is needed	☐ → Please describe the documentation required in the space below
Event is NOT adjudicated: CEC Members could not reach an agreement	☐ → The event will be adjudicated by the CEC Chair

Documentation required:

Section III: Comments

Please use the following space for any comments or remarks.

Adjudicator(s) signature

CEC Members

Please note: both CEC members are required to sign the form.

1. _____

2. _____

Place and date

_____

CEC Chair

(Please leave this section blank if the event has been adjudicated by the CEC Members.)

Place and date

<u>Vascular Death</u>: Event Adjudication Form

Patient ID: 0679 - _ _ _ - _ _ _
Event no. _ _ _
Patient YOB: _ _ _ _ (yyyy)
Site diagnosis: _____
Event date: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Adjudicators:

☐ CEC Members

1. Full name _____
2. Full name _____

☐ CEC Chair Full name _____

Date of adjudication: _ _ /_ _/_ _ _ _ (dd/mm/yyyy)

Vascular Death: Study definition

Vascular death is defined as:

- Any death that is due to a vascular cause.

Section I: Final Classification

Criteria for Vascular Death

Please note: the following criterion must be YES to adjudicate this event as “vascular death”.

	YES	NO/UNCERTAIN
Due to a vascular cause	☐ → Please specify the cause of death	☐

If you answered YES, please specify the cause of death.
Please check ONE only:

Sudden cardiac death	☐
Cardiac mechanical/pump failure	☐
Ischaemic stroke	☐
Haemorrhagic stroke	☐
Other major bleeding	☐
Clinically relevant non-major bleeding	☐
Systemic embolism	☐
Myocardial infarction	☐
Other vascular cause	☐ → Please specify: _____

Section II: Adjudication Decision
(Based on review of source documents)

Please check ONE only:

Event is adjudicated as vascular death	☐
Event CANNOT be adjudicated as vascular death	☐
Event is NOT adjudicated: More documentation is needed	☐ → Please describe the documentation required in the space below
Event is NOT adjudicated: CEC Members could not reach an agreement	☐ → The event will be adjudicated by the CEC Chair

Documentation required:

Section III: Comments

Please use the following space for any comments or remarks.

Adjudicator(s) signature

CEC Members

Please note: both CEC members are required to sign the form.

1. _____

2. _____

Place and date

_____

CEC Chair

(Please leave this section blank if the event has been adjudicated by the CEC Members.)

_____

Place and date

_____

References

[1] Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873-90.
[2] King G, Zeng L. Logistic regression in rare events data. Polit Anal 2001;9:137-63.
[3] Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:2.
[4] Paciaroni M, Agnelli G, Falocci N, et al. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. Stroke 2015;46:2175–82.