The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 29, 2023 VOL. 388 NO. 26

Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

U. Fischer, M. Koga, D. Strbian, M. Branca, S. Abend, S. Trelle, M. Paciaroni, G. Thomalla, P. Michel, K. Nedeltchev, L.H. Bonati, G. Ntaios, T. Gattringer, E.-C. Sandset, P. Kelly, R. Lemmens, P.N. Sylaja, D. Aguiar de Sousa, N.M. Bornstein, Z. Gdovinova, T. Yoshimoto, M. Tiainen, H. Thomas, M. Krishnan, G.C. Shim, C. Gumbinger, J. Vehoff, L. Zhang, K. Matsuzono, E. Kristoffersen, P. Desfontaines, P. Vanacker, A. Alonso, Y. Yakushiji, C. Kulyk, D. Hemelsoet, S. Poli, A. Paiva Nunes, N. Caracciolo, P. Slade, J. Demeestere, A. Salerno, M. Kneihsl, T. Kahles, D. Giudici, K. Tanaka, S. Räty, R. Hidalgo, D.J. Werring, M. Göldlin, M. Arnold, C. Ferrari, S. Beyeler, C. Fung, B.J. Weder, T. Tatlisumak, S. Fenzl, B. Rezny-Kasprzak, A. Hakim, G. Salanti, C. Bassetti, J. Gralla, D.J. Seiffge, T. Horvath, and J. Dawson, for the ELAN Investigators*

ABSTRACT

BACKGROUND

The effect of early as compared with later initiation of direct oral anticoagulants (DOACs) in persons with atrial fibrillation who have had an acute ischemic stroke is unclear.

METHODS

We performed an investigator-initiated, open-label trial at 103 sites in 15 countries. Participants were randomly assigned in a 1:1 ratio to early anticoagulation (within 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke) or later anticoagulation (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke). Assessors were unaware of the trial-group assignments. The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Secondary outcomes included the components of the composite primary outcome at 30 and 90 days.

RESULTS

Of 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke), 1006 were assigned to early anticoagulation and 1007 to later anticoagulation. A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group (risk difference, –1.18 percentage points; 95% confidence interval [CI], –2.84 to 0.47) by 30 days. Recurrent ischemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group (odds ratio, 0.57; 95% CI, 0.29 to 1.07) by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days (odds ratio, 0.60; 95% CI, 0.33 to 1.06). Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days.

CONCLUSIONS

In this trial, the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs. (Funded by the Swiss National Science Foundation and others; ELAN ClinicalTrials.gov number, NCT03148457.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fischer can be contacted at urs.fischer@usb.ch or at the Department of Neurology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

*A list of the ELAN Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 24, 2023, and updated on June 29, 2023, at NEJM.org.

N Engl J Med 2023;388:2411-21.
DOI: 10.1056/NEJMoa2303048

CME at NEJM.org

A Quick Take is available at NEJM.org

Anticoagulation with direct oral anticoagulants (DOACs) reduces the risk of ischemic stroke and systemic embolism among persons with atrial fibrillation.[1] However, whether the timing of DOAC initiation influences the risks of stroke recurrence and bleeding after an acute ischemic stroke is unclear. Early initiation may increase the risk of intracranial hemorrhage, whereas later initiation may increase the risk of early stroke recurrence.[1,2]

The risk of both recurrent ischemic stroke and intracranial hemorrhage is highest in the first few days after acute ischemic stroke, and although studies and small randomized trials suggest that early use of DOACs may be safe,[3-7] these investigations have had selection bias or small sample sizes. Given the lack of high-quality evidence, guideline recommendations regarding the timing of initiation of anticoagulation have varied. Some recommendations suggest initiation of anticoagulation at 1, 3, 6, or 12 days after a transient ischemic attack or after a minor, moderate, or severe ischemic stroke, respectively (the "1-3-6-12–day rule").[8] This guidance, which has been based on the observation that the risk of hemorrhagic transformation is related to infarct size,[9,10] is followed in many countries.[2,11,12] A neuroimaging-based risk-stratification approach may help to minimize the risk of intracranial hemorrhage.[9,10]

We conducted the Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN) randomized trial, which aimed to estimate the safety and efficacy of early initiation of DOACs as compared with later, guideline-based initiation, using imaging-based selection criteria in persons who have had a recent stroke and have atrial fibrillation.

Methods

Trial Design and Oversight

This international trial was overseen by University Hospital Bern and funded by the Swiss National Science Foundation and others. The trial protocol has been published previously[13] and is available with the full text of this article at NEJM.org. The protocol was approved by all responsible ethics committees and, if applicable, by the regulatory authorities in the countries in which the trial was conducted. The participant, next of kin or another legal representative, or an independent physician provided written informed consent before enrollment, according to country-specific requirements. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation E6 requirements and the Declaration of Helsinki.

The trial design, analysis, and data collection were overseen by a steering committee (see the Supplementary Appendix, available at NEJM.org). Site investigators gathered the data. Data analysis was performed by a trial statistician (the fourth author) who attests to the integrity of the analyses and the accuracy and completeness of the reported data. The steering committee and all the investigators vouch for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the accurate reporting of adverse events. The funding bodies had no role in the trial design; the collection, monitoring, analysis, or interpretation of the data; or the writing of the manuscript. There was no industry involvement in the trial.

Participants

The trial was conducted at 103 stroke centers in Europe, the Middle East, and Asia. Participants were eligible if they had had an ischemic stroke that had occurred within the time frames described below in the Trial Treatment section and if they had permanent, persistent, or paroxysmal nonvalvular atrial fibrillation or atrial fibrillation diagnosed during hospitalization for the stroke. To the best of our knowledge, all the participants with stroke were hospitalized.

Ischemic stroke was defined as evidence of acute cerebral infarction on magnetic resonance imaging (MRI) or computed tomography (CT) or as a clinical diagnosis of ischemic stroke with symptoms lasting more than 24 hours, confirmed by an investigator on the basis of a CT or an MRI scan that excluded other causes. Infarct size (minor, moderate, or major) was determined by the site investigators on the basis of imaging performed before randomization, with the use of a standardized visual rating scheme.[13-15] An infarct of 1.5 cm or smaller was defined as minor; an infarct in the distribution of a cortical superficial branch of the middle, anterior, or

posterior cerebral artery was defined as moderate; and larger infarcts in the distribution of these arteries or a brain-stem or cerebellar infarct larger than 1.5 cm were defined as major (Table S13 and Fig. S5 in the Supplementary Appendix).

Intravenous thrombolysis or thrombectomy before randomization was allowed, but therapeutic anticoagulation at stroke onset was not allowed, with the exception of prophylactic administration of low-molecular-weight heparin for the prevention of venous thromboembolism. Petechial hemorrhage within infarcted brain tissue was not an exclusion criterion for enrollment, but confluent parenchymal hematoma within infarcted brain tissue or intracranial hemorrhage remote from infarcted tissues was not allowed. Detailed eligibility criteria are provided in the protocol.

TRIAL TREATMENT

Participants were randomly assigned in a 1:1 ratio with the use of a centralized Web-based system to early initiation of DOAC or later initiation of DOAC. A deterministic minimization method[16] was used with the following stratification factors: age (<70 years or ≥70 years), infarct size (minor, moderate, or major), National Institutes of Health Stroke Scale (NIHSS) score (<10 or ≥10; range, 0 to 44, with higher scores indicating greater neurologic deficits), and trial site.

Any DOAC with marketing authorization for the prevention of stroke and systemic embolism in the trial-site country was allowed, at the appropriate dose. Early treatment was defined as initiation of a DOAC within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke. Later treatment was defined as initiation of a DOAC in participants with a minor stroke on day 3 or 4 after stroke onset, in participants with a moderate stroke on day 6 or 7, and in participants with a major stroke on day 12, 13, or 14. Participants in both groups continued to receive stroke care according to local standards.

OUTCOMES

The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Potential outcome events were identified through standardized telephone interviews by an assessor who was unaware of the trial-group assignments. When a potential event was detected, it was verified from the medical records by local investigators. An independent clinical events committee whose members were unaware of the trial-group assignments reviewed all potential outcome events for final adjudication. The clinical events committee classified deaths as having a vascular or nonvascular cause (see the Supplementary Appendix).

Secondary outcomes assessed at 30 and 90 days were the following: recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, vascular death, nonmajor bleeding, death from any cause, a binary outcome of a score of 0 to 2 versus 3 to 6 on the modified Rankin scale (a 7-point scale with a range from 0 to 6; scores of 0, 1, and 2 indicate slight or no disability and a score of 6 indicates death), and an ordinal shift in the distribution of scores on the modified Rankin scale between the two trial groups. The modified Rankin scale score at 90 days was obtained during a clinical visit or by a structured telephone interview. Major extracranial bleeding was defined as the occurrence of a decrease in the hemoglobin level of at least 2 g per deciliter over a 24-hour period, transfusion of 2 or more units of packed red cells, or bleeding in a critical part of the body (intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal) associated with a symptomatic clinical presentation.[17] These individual components of major extracranial bleeding were also secondary end points. Adverse events were assessed for up to 90 days. The incidence of composite primary-outcome events at day 90 was not prespecified as a secondary outcome, so these results should be considered exploratory.

STATISTICAL ANALYSIS

The main aim of the trial was to estimate the effect of early initiation as compared with later initiation of anticoagulation and to estimate the degree of precision of these estimates. Therefore, no statistical hypotheses as to superiority, inferiority, or noninferiority were tested. The sam-

ple size was calculated on the basis of the width of the expected confidence interval. With 1802 participants, we assumed that a primary-outcome event would occur in 5.0% of the participants in the control group (the later-treatment group) and 4.5% of those in the experimental group (the early-treatment group) within 30 days, and the expected width of the 95% confidence interval for the between-group difference would be at least 2.0 percentage points. This interval served as an anchor for planning but not as a noninferiority margin. To account for possible missing outcome data, we planned to enroll 2000 participants.

The primary analysis, which was based on the modified intention-to-treat principle (because of exclusion of one trial site, incorrect enrollment, or declined consent), involved all the enrolled participants according to their assigned treatment group who were not excluded. In the analysis of adverse events, which involved the participants according to the treatment they actually received, we estimated the safety of receiving at least one dose of early DOACs as compared with later DOACs. All stratification factors except trial site were included as covariates in all models.

The primary composite outcome was analyzed with the use of a penalized logistic-regression model to account for low event rates.[18] The risk difference with 95% confidence intervals was derived from the estimated odds ratio and its standard error. Outcomes for the participants who died from nonvascular causes without a preceding primary-outcome event were set to missing. Missing outcome data were imputed with the use of multivariate multiple imputation by chained equations for 50 imputed data sets on the basis of assignment and stratification factors. To support the interpretation of results, we performed a post hoc analysis using exchangeably weighted bootstrapping (with exponential weights) to calculate probabilities of early treatment being below a specific risk difference. This bootstrapping scheme used nonzero weights instead of resampling to avoid the problem of having no events in resamples.

Secondary binary outcomes were analyzed in the same way as the primary outcome, with the use of penalized logistic regression (dichotomized scores on the modified Rankin scale). Ordinal scores on the modified Rankin scale were analyzed with the use of ordinal logistic regression. Binary outcomes were also analyzed as time-to-event outcomes with the use of penalized survival models[19] to estimate cause-specific hazard ratios and nonparametric cumulative incidence, from which risk differences and the odds ratio were calculated. For the primary outcome only, subgroup analyses were performed for the stratification factors by introducing an interaction term with the treatment. Adverse events were summarized according to treatment group, as frequencies of participants with at least one event and the incidence rate.

Confidence intervals reflecting uncertainty in the estimates were not adjusted for multiplicity; therefore, they should not be interpreted as hypothesis tests. Full details of the statistical analyses are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS AND TREATMENT

A total of 36,643 participants were screened and 2032 participants were enrolled at 103 sites in 15 countries between November 6, 2017, and September 12, 2022. The distribution between the trial groups is shown in Figure 1 and Figure S6. Of these participants, 19 were excluded from the analysis; of these 19 participants, 13 had been enrolled at a trial site that had to be closed prematurely because of nonadherence to Good Clinical Practice guidelines, 5 declined to provide post hoc consent, and 1 underwent randomization twice (on the same occasion). This resulted in 2013 participants in the modified intention-to-treat population, 1006 of whom were assigned to early treatment and 1007 of whom were assigned to later treatment. Treatment was started according to the protocol in 949 participants in the early-treatment group and 935 participants in the later-treatment group. One participant in the early-treatment group was lost to follow-up at 30 days, and 2 participants in each group were lost to follow-up at 90 days.

Baseline demographic and clinical characteristics were similar in both treatment groups (Table 1). The median age was 77 years (interquartile range, 70 to 84), 915 participants (45%) were female, and the median NIHSS score was 5 (interquartile range, 2 to 11) at admission and 3 (interquartile range, 1 to 6) at randomization. According to imaging criteria, 38% of the par-

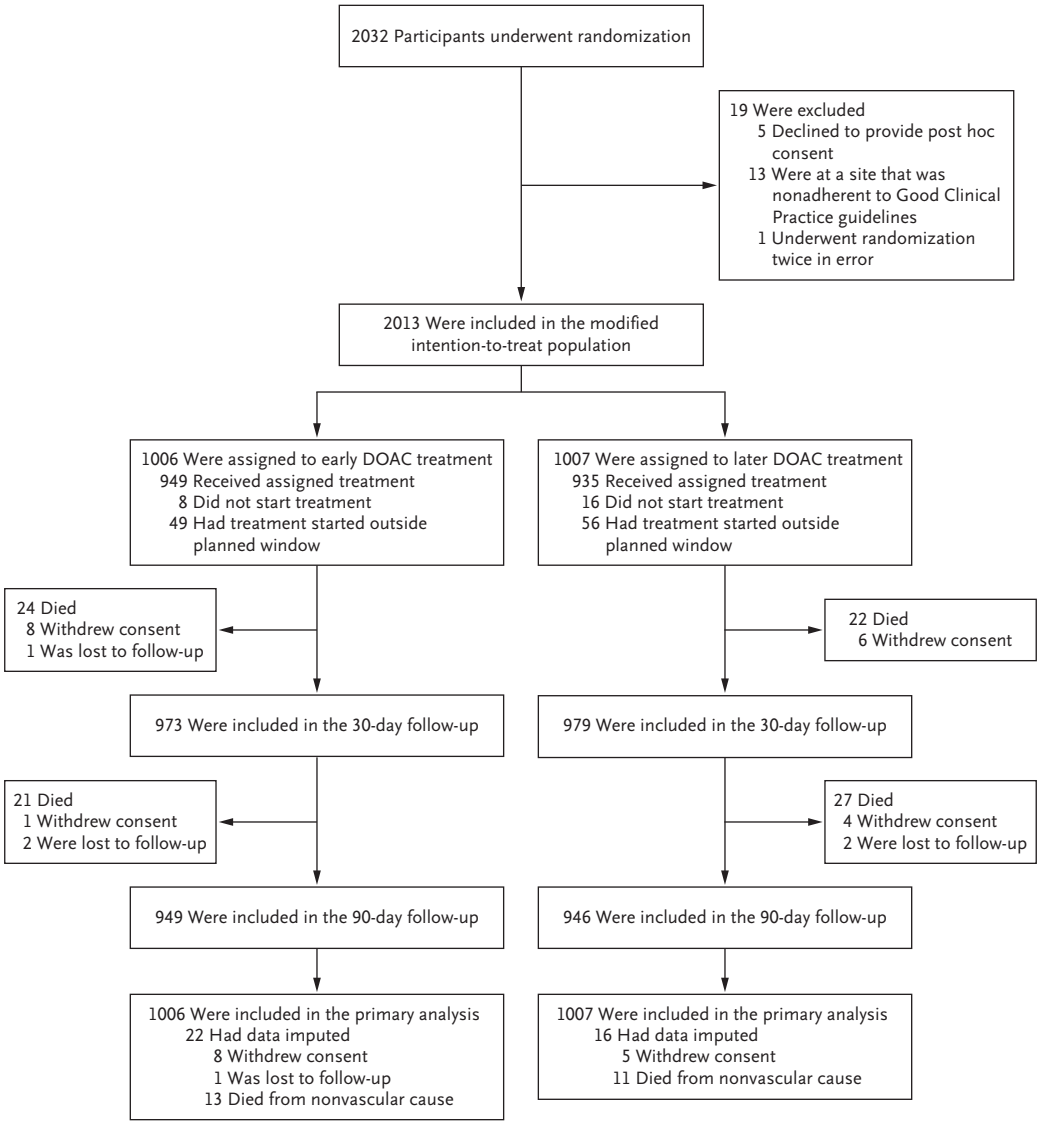

Figure 1. Randomization and Follow-up of the Participants in the Modified Intention-to-Treat Population.

The modified intention-to-treat population included all the participants who underwent randomization and were not subsequently excluded. One death (in the later-treatment group) that occurred at day 99 after randomization is shown here because it was a consequence of an ongoing serious adverse event during the last visit. It is not counted in the secondary outcomes. DOAC denotes direct oral anticoagulant.

ticipants in the early-treatment group and 37% in the later-treatment group had had a minor stroke; 40% and 39%, respectively, had had a moderate stroke; and 23% in each group had had a major stroke. The representativeness of the trial participants is summarized in Table S12. Approximately 50% of the participants were receiving aspirin at the time of screening. Details of the imaging findings at baseline are provided in Table S1, and details regarding the DOACs used and doses are provided in Table S2.

PRIMARY OUTCOME

Primary-outcome data were available for 1975 of 2013 participants (98%). A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and in 41 participants (4.1%) in the later-treatment group. The estimated

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Early-Treatment Group (N = 1006)	Later-Treatment Group (N = 1007)
Median age (IQR) — yr	77 (70–84)	78 (71–84)
Female sex — no. (%)	459 (45.6)	456 (45.3)
Region — no. (%)		
Central Europe	615 (61.1)	618 (61.4)
United Kingdom and Ireland	249 (24.8)	250 (24.8)
Israel	17 (1.7)	17 (1.7)
India	26 (2.6)	29 (2.9)
Japan	99 (9.8)	93 (9.2)
Medical history — no. (%)		
Ischemic stroke	128 (12.7)	140 (13.9)
Transient ischemic attack	45 (4.5)	51 (5.1)
Systemic embolism	19 (1.9)	31 (3.1)
Hypertension	690 (68.6)	673 (66.8)
Myocardial infarction	80 (8.0)	87 (8.6)
Diabetes	185 (18.4)	161 (16.0)
Median CHA_2DS_2-VASc score (IQR)†	5 (4–6)	5 (4–6)
Prestroke score on the modified Rankin scale — no./total no. (%)‡§		
0–2	889/1005 (88.5)	898/1006 (89.3)
3–5	116/1006 (11.5)	108/1007 (10.7)
Stroke severity according to infarct size — no. (%)		
Minor	378 (37.6)	374 (37.1)
Moderate	399 (39.7)	397 (39.4)
Major	229 (22.8)	236 (23.4)
NIHSS score — median (IQR)§		
At admission¶	5 (2–12)	5 (2–11)
At time of randomization	3 (1–6)	3 (1–6)
Initial treatment for stroke — no./total no. (%)¶		
Thrombolysis	391/986 (39.7)	377/987 (38.2)
Thrombectomy	207/986 (21.0)	232/987 (23.5)

* IQR denotes interquartile range.
† The CHA_2DS_2-VASc score (an assessment of the risk of stroke among patients with atrial fibrillation according to congestive heart failure, hypertension, age >75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, and sex) ranges from 0 to 9, with 0 indicating no risk and 9 indicating a very high stroke risk.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with 0 indicating no deficits and a higher score indicating more severe neurologic symptoms.
§ Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death).
¶ Data on NIHSS scores at admission were missing for 25 participants in the early-treatment group and 24 participants in the later-treatment group.

odds ratio for a primary-outcome event in the early-treatment group as compared with the later-treatment group was 0.70 (95% confidence interval [CI], 0.44 to 1.14), and the derived risk difference was –1.18 percentage points (95% CI, –2.84 to 0.47) (Fig. 2). Death from non–vascular causes before 30 days occurred in 13 participants in the early-treatment group and in 11 participants in the later-treatment group.

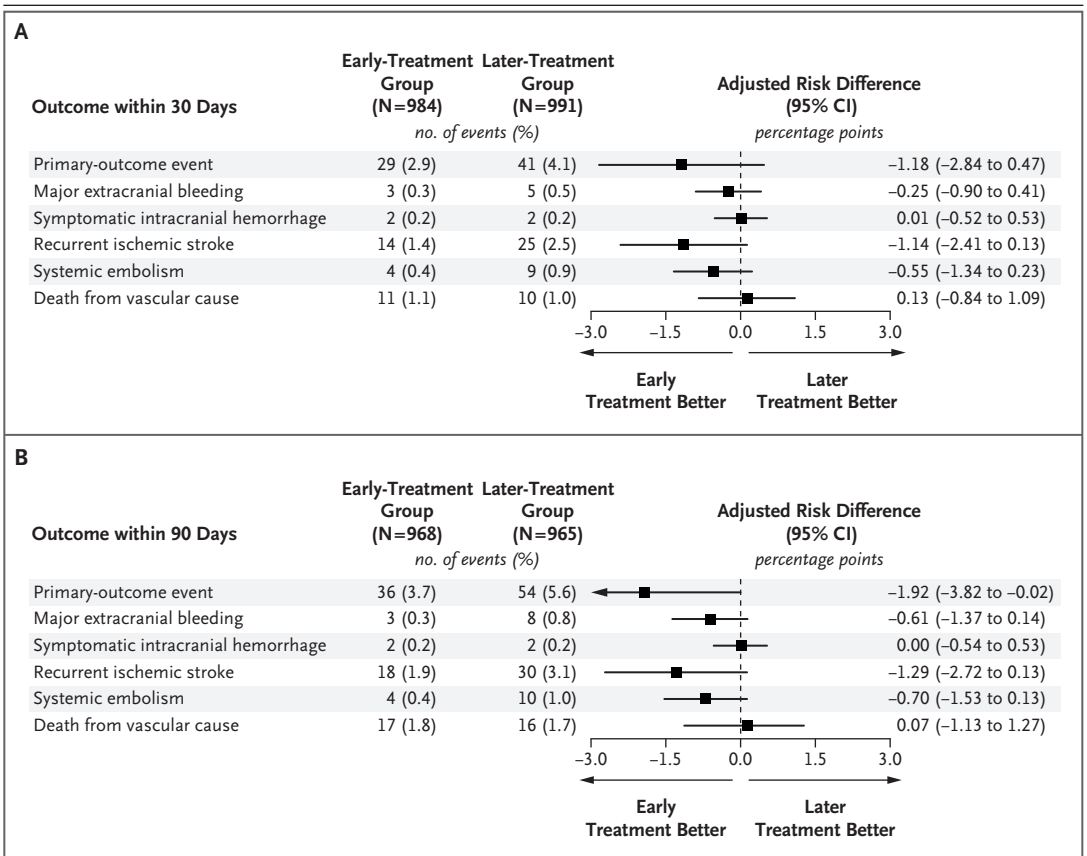

Figure 2. The Primary Composite Outcome and Its Components at 30 and 90 Days.

Shown are point estimates (squares) and two-sided 95% confidence intervals (horizontal bars) for the treatment effect, which was defined as a risk difference between the trial groups (early initiation of DOAC minus later initiation of DOAC). The absolute and relative numbers of events in each group are shown. The risk difference is derived from a penalized logistic regression adjusted for stratification factors. The widths of the confidence intervals were not adjusted for multiple comparisons, and the reported confidence intervals should not be used for hypothesis testing.

SECONDARY OUTCOMES

Major extracranial bleeding by 30 days after randomization occurred in 3 participants (0.3%) in the early-treatment group and 5 participants (0.5%) in the later-treatment group (odds ratio, 0.63; 95% CI, 0.15 to 2.38). Symptomatic intracranial hemorrhage by 30 days occurred in 2 participants (0.2%) in both groups (odds ratio, 1.02; 95% CI, 0.16 to 6.59). Recurrent ischemic stroke by 30 days occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group (odds ratio, 0.57; 95% CI, 0.29 to 1.07) (Table 2 and Fig. 2).

The incidence of a composite-outcome event (recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death) at 90 days was 3.7% in the early-treatment group and 5.6% in the later-treatment treatment group (odds ratio, 0.65; 95% CI, 0.42 to 0.99); this was not prespecified as a secondary outcome, so these results should be considered exploratory. The cumulative rates of recurrent ischemic stroke at 90 days were 1.9% in the early-treatment group and 3.1% in the later-treatment group (odds ratio, 0.60; 95% CI, 0.33 to 1.06). The incidence of symptomatic intracranial hemorrhage was 0.2% in both groups (odds ratio, 1.00; 95% CI, 0.15 to 6.45). Other secondary outcomes at 30 and 90 days are shown in Table 2 and Table S6. Time-to-event analyses of binary outcomes, including recurrent ischemic stroke through 90 days, are shown in Table S8. Figure S1 shows the cumulative probabilities for risk-difference thresholds for the primary outcome and its components. The curve in Figure S1A indicates a 98%

Table 2. Primary and Secondary Efficacy Outcomes.

Outcome	Early-Treatment Group (N=1006)	Later-Treatment Group (N=1007)	Adjusted Odds Ratio (95% CI)*
	no./total no. (%)		
Primary outcome: composite outcome at 30 days	29/1006 (2.9)†	41/1007 (4.1)†	0.70 (0.44 to 1.14)‡
Secondary outcomes at 30 days			
Major extracranial bleeding	3/984 (0.3)	5/991 (0.5)	0.63 (0.15 to 2.38)
Symptomatic intracranial hemorrhage	2/984 (0.2)	2/991 (0.2)	1.02 (0.16 to 6.59)
Recurrent ischemic stroke	14/984 (1.4)	25/991 (2.5)	0.57 (0.29 to 1.07)
Systemic embolism	4/984 (0.4)	9/991 (0.9)	0.48 (0.14 to 1.42)
Vascular death	11/984 (1.1)	10/991 (1.0)	1.12 (0.47 to 2.65)
Nonmajor bleeding	30/984 (3.0)	27/991 (2.7)	1.13 (0.67 to 1.93)
Modified Rankin scale score ≤2§	624/997 (62.6)	626/1000 (62.6)	0.93 (0.79 to 1.09)
Secondary outcomes at 90 days			
Major extracranial bleeding	3/968 (0.3)	8/965 (0.8)	0.40 (0.10 to 1.31)
Symptomatic intracranial hemorrhage	2/968 (0.2)	2/965 (0.2)	1.00 (0.15 to 6.45)
Recurrent ischemic stroke	18/968 (1.9)	30/965 (3.1)	0.60 (0.33 to 1.06)
Systemic embolism	4/968 (0.4)	10/965 (1.0)	0.42 (0.12 to 1.21)
Vascular death	17/968 (1.8)	16/965 (1.7)	1.04 (0.52 to 2.08)
Death from any cause¶	45/994 (4.5)	48/995 (4.8)	0.93 (0.61 to 1.43)
Nonmajor bleeding	39/968 (4.0)	41/965 (4.2)	0.94 (0.59 to 1.47)
Modified Rankin scale score ≤2§	659/989 (66.6)	654/994 (65.8)	0.93 (0.79 to 1.09)
Any serious adverse event‖	132/947 (13.9)	157/993 (15.8)	

* The analyses were stratified according to or adjusted for age, NIHSS score at admission, and infarct size. The widths of the 95% confidence intervals (CIs) were not adjusted for multiple comparisons and should therefore not be used for inference about treatment effects.
† For the estimation of the primary outcome, data on 22 participants in the early-treatment group and 16 participants in the later-treatment group were imputed.
‡ The between-group risk difference for the primary outcome was –1.18 percentage points (–2.84 to 0.47).
§ The modified Rankin scale was analyzed with the use of ordinal logistic regression, and the incidences and percentages shown are the values of 2 or less.
¶ One death occurred at day 99 after randomization; therefore, it is not counted in the secondary outcomes.
‖ An odds ratio was not provided for this outcome because it was not calculated with the same methods used to calculate the other outcomes.

probability that early treatment with DOACs would increase the risk of a primary-outcome event by no more than 0.5 percentage points, and Figure S1B shows these probabilities for the components of the primary outcome.

SAFETY

Any serious adverse event by 90 days occurred in 132 participants (13.9%) in the early-treatment group and 157 participants (15.8%) in the later-treatment group (Table 2). Further details regarding adverse events are provided in Tables S3 through S5.

SENSITIVITY, PER-PROTOCOL, AND SUBGROUP ANALYSES

The sensitivity analyses of the primary outcome under several assumptions and with the use of different statistical models showed results that were similar to those of the primary analysis (Table S7). Results for the primary and secondary outcomes in the per-protocol population were similar to those in the main analysis (Table S9). No apparent heterogeneity of effects across prespecified subgroups with the use of treatment-by-covariate terms was observed, but the trial was not powered to analyze subgroups and

there was no correction of the widths of confidence intervals for multiple comparisons (Fig. S2).

DISCUSSION

This trial was designed to estimate the treatment effects of early initiation and later initiation of DOACs and the degree of precision of this estimate. No statistical hypothesis was tested for superiority or noninferiority, and the results are intended to provide qualitative data that may be of use to clinicians. The components of the primary outcome that are probably of most interest to clinicians are recurrent ischemic strokes, systemic embolism, and symptomatic intracranial hemorrhage. By day 30, recurrent ischemic strokes had occurred in 1.4% of the participants in the early-treatment group and 2.5% of the participants in the later-treatment group; systemic embolism had occurred in 0.4% and 0.9%, respectively; and the incidence of symptomatic intracranial hemorrhage was low, approximately 0.2% in both treatment groups. On the basis of the widths of the 95% confidence intervals, our data are consistent with treatment effects (defined as the difference in the incidence of the primary outcome with early treatment as compared with later treatment) that range from a reduction of approximately 2.8 percentage points to an increase of 0.5 percentage points in the risk of a primary-outcome event. Early treatment initiation can therefore be supported if indicated or if desired. The rates of the outcomes increased only slightly more at 90 days than at 30 days, findings that suggest there was not an excessive risk associated with early anticoagulation through that period.

Current clinical practice is to delay the initiation of anticoagulation after ischemic stroke, as recommended in several guidelines that are based on expert consensus. For example, European guidelines suggest assessment of stroke severity with the use of the NIHSS score and delay of anticoagulation for 3 days after minor stroke, 6 days after moderate stroke, and 12 days after severe stroke on the basis of this score. American Heart Association–American Stroke Association guidelines[20] recommend delaying anticoagulation beyond 14 days if there is a high risk of hemorrhagic transformation of an ischemic brain infarct and beginning anticoagulation between day 2 and day 14 if the risk of this complication is low. We studied initiation of DOACs within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke.

We chose to use an imaging-based definition of stroke severity because an alternative, the NIHSS score, is dependent on both the location and size of the infarct. In several studies, the size of an infarct measured by volume analysis or semiquantitative measures has been related to the risk of hemorrhagic transformation.[10] Our data suggest that the incidence of symptomatic intracranial hemorrhage is low with early anticoagulation if imaging-based classification is used. Further research is needed to confirm whether this remains the case with NIHSS-based definitions of infarct severity and whether persons with atrial fibrillation and severe ischemic stroke can receive anticoagulation earlier than 6 days after symptom onset.

Our trial is one of several randomized, controlled trials comparing early anticoagulation with later anticoagulation with DOACs in persons with acute stroke and atrial fibrillation. Our trial differs from the TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke with Atrial Fibrillation)[21] trial in Sweden and the ongoing OPTIMAS (Optimal Timing of Anticoagulation after Acute Ischaemic Stroke) trial (ClinicalTrials.gov number, NCT03759938) in the United Kingdom in that our participants underwent randomization within 48 hours after a minor or moderate stroke, we used an imaging-based approach, and we compared early initiation with the 1-3-6-12–day rule, which is widely used. Furthermore, the aim of the TIMING and OPTIMAS trials was to test noninferiority with a nested test of superiority. The TIMING trial was terminated prematurely owing to slow recruitment after 888 participants had undergone randomization.[19] The results of our trial are generally similar to those of the TIMING trial.

The limitations of our trial are the exclusion of persons who were already receiving therapeutic anticoagulation at baseline and the low median NIHSS score at randomization. The trial also has limited statistical power to explore subgroups, and therefore no conclusions can be drawn from these results. We do not have data on the ethnic group and race of the participants.

The trial population was predominantly from European centers, which have a high proportion of White participants. Extrapolation of the results to other populations may not be possible. We did not centrally adjudicate the classification of stroke severity. Finally, persons with parenchymal hemorrhage type 1 or 2 in the Heidelberg classification (hemorrhagic transformation within or within and beyond the region of the infarct) at the time of randomization were not included in this trial, so we cannot comment on the safety of early anticoagulation in this group.

We estimated the risks of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, and vascular death with early or later initiation of DOACs among persons with recent ischemic stroke and atrial fibrillation, using imaging as a guide to the timing of treatment within each trial group. The incidence of the composite of stroke, systemic embolism, hemorrhage, or death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early use of DOACs than with later use.

Supported by grants from the Swiss National Science Foundation (32003B_197009; 32003B_169975), the Swiss Heart Foundation, the Stroke Association in the United Kingdom (2017/02), and the Intramural Research Fund (20-4-5) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center, Japan.

Disclosure forms provided by the authors are available at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Urs Fischer, M.D., Masatoshi Koga, M.D., Ph.D., Daniel Strbian, Ph.D., Mattia Branca, Ph.D., Stefanie Abend, B.Sc., Sven Trelle, M.D., Maurizio Paciaroni, M.D., Götz Thomalla, M.D., Patrik Michel, M.D., Krassen Nedeltchev, M.D., Leo H. Bonati, M.D., George Ntaios, M.D., Thomas Gattringer, Ph.D., Else-Charlotte Sandset, Ph.D., Peter Kelly, M.D., Robin Lemmens, Ph.D., P.N. Sylaja, M.D., Diana Aguiar de Sousa, Ph.D., Natan M. Bornstein, M.D., Zuzana Gdovinova, M.D., Ph.D., Takeshi Yoshimoto, M.D., Ph.D., Marjaana Tiainen, M.D., Ph.D., Helen Thomas, R.N., Manju Krishnan, M.B., B.S., Gek C. Shim, M.B., B.Ch., Christoph Gumbinger, M.D., Jochen Vehoff, M.D., Liqun Zhang, M.D., Ph.D., Kosuke Matsuzono, M.D., Ph.D., Espen Kristoffersen, M.D., Ph.D., Philippe Desfontaines, M.D., Peter Vanacker, M.D., Ph.D., Angelika Alonso, M.D., Yusuke Yakushiji, M.D., Ph.D., Caterina Kulyk, M.D., Dimitri Hemelsoet, M.D., Sven Poli, M.D., Ana Paiva Nunes, M.D., Nicoletta Caracciolo, M.D., Peter Slade, M.B., B.Ch., Jelle Demeestere, M.D., Ph.D., Alexander Salerno, M.D., Markus Kneihsl, M.D., Ph.D., Timo Kahles, M.D., Daria Giudici, M.D., Kanta Tanaka, M.D., Ph.D., Silja Räty, M.D., Ph.D., Rea Hidalgo, R.N., David J. Werring, F.R.C.P., Ph.D., Martina Göldlin, M.D., Marcel Arnold, M.D., Cecilia Ferrari, M.B.A.-I.H.M., Seraina Beyeler, Ph.D., Christian Fung, M.D., Bruno J. Weder, M.D., Turgut Tatlisumak, M.D., Ph.D., Sabine Fenzl, M.D., Beata Rezny-Kasprzak, M.D., Arsany Hakim, M.D., Georgia Salanti, Ph.D., Claudio Bassetti, M.D., Jan Gralla, M.D., David J. Seiffge, M.D., Thomas Horvath, M.D., and Jesse Dawson, M.D.

The authors' affiliations are as follows: the Department of Neurology, University Hospital Basel, University of Basel, Basel (U.F., T.K.), the Department of Neurology (U.F., S.A., K.N., M.G., M.A., C. Ferrari, S.B., C.B., D.J.S., T.H.), the Support Center for Advanced Neuroimaging, Institute of Diagnostic and Interventional Neuroradiology (B.J.W.), and the Institute for Diagnostic and Interventional Neuroradiology (S.F., B.R.-K., A.H., J.G.), University Hospital Bern, and CTU Bern (M.B., S.T.), Institute of Social and Preventive Medicine (G.S.), University of Bern, Bern, the Department of Neurology, University Hospital Lausanne, University of Lausanne, Lausanne (P.M., A.S.), the Department of Neurology, Cantonal Hospital Aarau, Aarau (K.N., T.K.), the Research Department, Reha Rheinfelden, Rheinfelden (L.H.B.), and the Department of Neurology, Cantonal Hospital St. Gallen, St. Gallen (J.V.) — all in Switzerland; the Departments of Cerebrovascular Medicine (M. Koga, K.T.) and Neurology (T.Y.), National Cerebral and Cardiovascular Center, Osaka, the Division of Neurology, Department of Medicine, Jichi Medical University, Tochigi (K.M.), and the Department of Neurology, Kansai Medical University, Hirakata (Y.Y.) — all in Japan; the Department of Neurology, Helsinki University Hospital, and University of Helsinki, Helsinki (D.S., M.T., S.R.); Internal, Vascular, and Emergency Medicine, Stroke Unit, Santa Maria della Misericordia Hospital, University of Perugia, Perugia (M.P., D.G.), and the Department of Human Neurosciences, University La Sapienza, Rome (N.C.) — both in Italy; the Department of Neurology, University Medical Center Hamburg–Eppendorf, Hamburg (G.T.), the Department of Neurology, Heidelberg University Hospital (C.G.), and the Department of Neurology, Medical Faculty Mannheim, University of Heidelberg (A.A.), Heidelberg, the Department of Neurology and Stroke and the Hertie Institute for Clinical Brain Research, Tübingen University, Tübingen (S.P.), and the Department of Neurosurgery, Medical Center, University of Freiburg, Freiburg (C. Fung) — all in Germany; the Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece (G.N.); the Department of Neurology, and the Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology, Medical University of Graz, Graz (T.G., M. Kneihsl), and the Department of Neurology 2, Kepler University Hospital, Johannes Kepler University, Linz (C.K.) — both in Austria; the Department of Neurology, Oslo University Hospital (E.-C.S.), the Department of General Practice, University of Oslo (E.K.), and the Norwegian Air Ambulance Foundation (E.-C.S.), Oslo, and the Department of Neurology, Akershus University Hospital, Lørenskog (E.K.) — all in Norway; the Department of Neurology, Mater Misericordiae University Hospital, Dublin (P.K.); KU Leuven, Department of Neurosciences, Experimental Neurology, and the Department of Neurology, University Hospitals Leuven, Leuven (R.L., J. Demeestere), the Department of Neurology, Comprehensive Stroke Unit, CHC MontLégia Hospital, Liège (P.D.), the Department of Neurology, Algemeen Ziekenhuis Groeninge Kortrijk, Kortrijk (P.V.), the Neurovascular Center and Stroke Unit Antwerp, Antwerp University Hospital, and the Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp (P.V.), and the Department of Neurology, Ghent University Hospital, Ghent (D.H.) — all in Belgium; Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India (P.N.S.); the Stroke Center, Lisbon Central University Hospital (D.A.S., A.P.N.) and Faculty of Medicine, University of Lisbon (D.A.S.) — both in Lisbon, Portugal; the Department of Neurology, Shaare Zedek Medical Center, Jerusalem (N.M.B.); the Department of Neurology, Faculty of Medicine, Pavol Jozef Safarik University, and University

Hospital Louis Pasteur — both in Košice, Slovakia (Z.G.); Glan Clwyd Hospital, Betsi Cadwaladr University Health Board, Rhyl (H.T., R.H.), the Stroke Unit, Morriston Hospital, Swansea Bay University Health Board, Swansea (M. Krishnan, P.S.), the Stroke Department, University Hospital of North Durham, Durham (G.C.S.), the Department of Neurology, St. George's University Hospital (L.Z.), and the Stroke Research Centre, Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology, University College London (D.J.W.), London, and the School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow (J. Dawson) — all in the United Kingdom; and the Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, and the Department of Neurology, Sahlgrenska University Hospital — both in Gothenburg, Sweden (T.T.).

REFERENCES

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
2. Seiffge DJ, Werring DJ, Paciaroni M, et al. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. Lancet Neurol 2019;18:117-26.
3. Seiffge DJ, Traenka C, Polymeris A, et al. Early start of DOAC after ischemic stroke: risk of intracranial hemorrhage and recurrent events. Neurology 2016;87:1856-62.
4. Seiffge DJ, Paciaroni M, Wilson D, et al. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. Ann Neurol 2019;85:823-34.
5. Abdul-Rahim AH, Fulton RL, Frank B, et al. Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: analysis from VISTA. Eur J Neurol 2015;22:1048-55.
6. De Marchis GM, Seiffge DJ, Schaedelin S, et al. Early versus late start of direct oral anticoagulants after acute ischaemic stroke linked to atrial fibrillation: an observational study and individual patient data pooled analysis. J Neurol Neurosurg Psychiatry 2022;93:119-25.
7. Hong K-S, Kwon SU, Lee SH, et al. Rivaroxaban vs warfarin sodium in the ultra-early period after atrial fibrillation-related mild ischemic stroke: a randomized clinical trial. JAMA Neurol 2017;74:1206-15.
8. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 2013;34:2094-106.
9. Paciaroni M, Agnelli G, Ageno W, Caso V. Timing of anticoagulation therapy in patients with acute ischaemic stroke and atrial fibrillation. Thromb Haemost 2016;116:410-6.
10. Paciaroni M, Agnelli G, Falocci N, et al. Early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with non-vitamin-K oral anticoagulants (RAF-NOACs) study. J Am Heart Assoc 2017;6(12):e007034.
11. Klijn CJ, Paciaroni M, Berge E, et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: a European Stroke Organisation guideline. Eur Stroke J 2019;4:198-223.
12. Jung S, Mattle H, Horvath T. Stroke guidelines of the Bern Stroke Network. Bern University Hospital, 2021 (http://www.neurologie.insel.ch/fileadmin/Neurologie/Dokumente/Stroke_Center/Stroke_Guidelines_2021_English.pdf).
13. Fischer U, Trelle S, Branca M, et al. Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillatioN (ELAN): protocol for an international, multicentre, randomised-controlled, two-arm, open, assessor-blinded trial. Eur Stroke J 2022;7:487-95.
14. Mustanoja S, Haapaniemi E, Putaala J, Strbian D, Kaste M, Tatlisumak T. Haemorrhagic transformation of ischaemic stroke in young adults. Int J Stroke 2014;9:Suppl A100:85-92.
15. Paciaroni M, Agnelli G, Corea F, et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008;39:2249-56.
16. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.
17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692-4.
18. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:27-38.
19. Ambler G, Seaman S, Omar RZ. An evaluation of penalised survival methods for developing prognostic models with rare events. Stat Med 2012;31:1150-61.
20. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52(7):e364-e467.
21. Oldgren J, Åsberg S, Hijazi Z, et al. Early versus delayed non-vitamin k antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled noninferiority study. Circulation 2022;146:1056-66.