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# Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation

## A Pragmatic, Response-Adaptive Randomized Clinical Trial

Steven J. Warach, MD, PhD; Lisa A. Davis, RN, PhD; Patrick Lawrence, BS; Byron Gajewski, PhD; Jo Wick, PhD; Fred Shi, PhD; Ty T. Shang, MD, PhD; DaiWai M. Olson, PhD; Sidarrth Prasad, MBBS; Lee Birnbaum, MD; Jody M. Richardson, MSN; Sean I. Savitz, MD; Mark P. Goldberg, MD; Salvador Cruz-Flores, MD; Israel Alba, MBA; Jane Anderson, PhD; Barbara Kimmel, PhD; Chethan P. Venkatasubba Rao, MD; Ben King, PhD; Adrienne N. Dula, PhD; Truman J. Milling, MD

**IMPORTANCE** Clinical practice guidelines recommend initiation of anticoagulation within 2 weeks after stroke with atrial fibrillation. It is unknown whether there is an optimal starting day within the 14-day period that balances the risks of recurrent embolic events against serious hemorrhagic events.

**OBJECTIVE** To determine if there is an optimal delay time to initiate treatment with a direct oral anticoagulant after atrial fibrillation–related stroke that minimizes the risk of a composite outcome of ischemic or hemorrhagic events.

**DESIGN, SETTING, AND PARTICIPANTS** This phase 2, pragmatic, response-adaptive randomized clinical trial was conducted between June 2017 and June 2023 at acute care hospitals in Texas and included patients who had a mild to moderate ischemic stroke (minimum lesion diameter of 1.5 cm) with atrial fibrillation and were prescribed a direct oral anticoagulant within 2 weeks from stroke onset.

**INTERVENTION** Within 3 to 4 days after atrial fibrillation–associated ischemic stroke, patients were randomized to a group for treatment start date (group 1 was day 3 or 4 after stoke onset; group 2 was day 6; group 3 was day 10; and group 4 was day 14) with a direct oral anticoagulant for secondary stroke prevention.

**MAIN OUTCOMES AND MEASURES** The composite primary outcome was an ischemic (stroke or systemic embolism) or hemorrhagic (symptomatic intracranial hemorrhage or major systemic hemorrhage) event observed within 30 days from the index stroke time of onset. Posterior probabilities were used to estimate which timing groups were optimal for treatment initiation and were recalculated at predefined intervals. The randomization allocations were adjusted to favor the groups with higher probabilities.

**RESULTS** The trial enrolled and randomized 200 patients (50% were female; the median age was 75 years [IQR, 65-81 years]; 17.5% were Asian, Black, or >1 race; 16.5% were Hispanic; the median National Institutes of Health Stroke Scale score was 6.5 [IQR, 4-14]; and the median lesion diameter was 3.1 cm [IQR, 2.0-4.4 cm]). No ischemic events were observed for group 1, 3 events were observed for group 2, 2 events were observed for group 3, and 2 events were observed for group 4. One hemorrhagic event was observed for group 1, 1 event was observed for group 2, 1 event was observed for group 3, and 0 events were observed for group 4. Group 1 had a posterior probability of 0.41 for being the optimal day for treatment initiation and it was 0.26 for group 2, 0.17 for group 3, and 0.15 for group 4. The use of response-adaptive randomization was feasible and favored groups with earlier initiation times for use of a direct oral anticoagulant.

**CONCLUSIONS AND RELEVANCE** A clearly superior day to initiate use of a direct oral anticoagulant for secondary stroke prevention in patients with atrial fibrillation was not identified, but the evidence suggests that initiating use of a direct oral anticoagulant earlier is better than at later times within the first 2 weeks after stroke onset.

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Multimedia

Supplemental content

**Author Affiliations:** Dell Medical School, University of Texas at Austin (Warach, Davis, Lawrence, Dula, Milling); Kansas University Medical Center, Kansas City (Gajewski, Wick, Shi); UT Southwestern Medical Center, Dallas, Texas (Shang, Olson, Prasad); UT Health Science Center, San Antonio, Texas (Birnbaum, Richardson, Goldberg); Stroke Institute, UT Health, Houston, Texas (Savitz); Texas Tech University Health Sciences Center, El Paso (Cruz-Flores, Alba); Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (Anderson); Baylor College of Medicine, Houston, Texas (Kimmel, Venkatasubba Rao); Tilman J. Fertitta Family College of Medicine, University of Houston, Houston, Texas (King).

**Corresponding Author:** Steven J. Warach, MD, PhD, Department of Neurology, Dell Medical School, University of Texas at Austin, 1601A Trinity St, Austin, TX 78712 (steven.warach@austin.utexas.edu).

Long-term oral anticoagulation is the standard treatment for secondary stroke prevention in patients with atrial fibrillation (AF), but carries the risk of hemorrhagic transformation. Since 2006, the American Heart Association/American Stroke Association clinical practice guidelines[1-3] have recommended that, for patients at low risk for hemorrhagic conversion, it may be reasonable to initiate oral anticoagulation after ischemic stroke due to nonvalvular AF within the first 2 weeks after ischemic stroke to reduce the risk of recurrent stroke. However, there is limited data on the optimal timing to start anticoagulation within those first 2 weeks. The data upon which the guideline recommendation was based were derived primarily from anticoagulation with heparins and vitamin K antagonists (eg, warfarin).[4]

The use of direct oral anticoagulants has since become preferred as secondary stroke prophylaxis in patients with AF,[2] so the question of optimal timing of direct oral anticoagulant initiation is of increased interest because direct oral anticoagulants may have different risk and benefit profiles than heparins and vitamin K antagonists.[5,6] To investigate whether one start day was superior to others in reducing the composite end point of ischemic or hemorrhagic events, we conducted a response-adaptive randomized clinical trial of 4 delay times (day 3 or 4 from stroke onset, day 6, day 10, or day 14) to start of a direct oral anticoagulant within the first 14 days after ischemic stroke due to AF-associated stroke. Response-adaptive randomization trials place more participants in better-performing groups and have been used to compare multiple interventions.[7]

### Key Points

**Question** Is there an optimal day within the first 14 days to initiate anticoagulation with a direct oral anticoagulant after atrial fibrillation–associated acute ischemic stroke?

**Findings** In this phase 2, response-adaptive randomized clinical trial, none of the 4 groups met statistical criteria as the optimal day for treatment initiation. Group 1 (initiation of a direct oral anticoagulant 3-4 days after atrial fibrillation–associated ischemic stroke for secondary stroke prevention) had no ischemic events and the highest posterior probability (0.41) of being optimal for treatment initiation.

**Meaning** Although a clearly superior day to initiate use of a direct oral anticoagulant was not identified, the evidence suggests that initiating a direct oral anticoagulant earlier is better than later within the first 2 weeks after stroke due to atrial fibrillation.

## Methods

START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation) was a prospective, pragmatic, multicenter, parallel-group, time to treatment, response-adaptive, randomized clinical trial including patients with mild to moderate ischemic stroke severity attributed to nonvalvular AF. A pragmatic design was chosen to allow the results to be directly applicable to clinical practice and to minimize the burden of data collection and reporting by investigators beyond the data fields required to determine eligibility and outcome events of interest. The trial protocol appears in Supplement 1. The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline was used.

Patients were randomized to start treatment within the 14-day period after stroke that is recommended by current clinical practice guidelines. The selection of direct oral anticoagulant, dose, and concomitant use of antiplatelet medicines was made at the discretion of the clinicians. Patients were recruited from inpatient settings at 10 stroke centers participating in the Lone Star Stroke Research Consortium. After consent was obtained and randomization, only members of the clinical care team interacted with participants. Study personnel conducted the 30- and 90-day telephone follow-up visits.

Inclusion and exclusion criteria appear in the **Box**. Patients with mild to moderate stroke severity were selected by including only (1) individuals with infarcts that were at least 1.5 cm in diameter on screening brain imaging or (2) individuals with a National Institutes of Health Stroke Scale (NIHSS) score of greater than 4 if the infarct was not evident. Patients were excluded if they had (1) infarcts with an estimated volume greater than half of the middle cerebral artery territory or (2) a NIHSS score greater than 23 if the infarct was not apparent on imaging. Additional information on the background and the methods used appears in the eMethods in Supplement 2.

### Intervention

Within 72 hours from the time patients were last known to be well, individuals were randomized to begin direct oral anticoagulant treatment in 1 of 4 groups (day 3 or 4 from stroke onset [group 1], day 6 [group 2], day 10 [group 3], or day 14 [group 4]) (**Figure**). The window for group 1 was expanded from 3 days to 4 days (48-96 hours) because the inpatient workups used to decide whether to prescribe a direct oral anticoagulant were often not completed within 72 hours from the time last known to be well; therefore, the window for randomization was increased to 96 hours.

The trial was initially designed with a sample size of 1000 patients based on simulations of the response-adaptive randomization design, assuming an average composite primary outcome rate of 10% under various outcome conditions.[4,8] Because of slower than anticipated enrollment and funding limitations, the target sample size was changed via a protocol amendment to 200 patients, which was made after 83 patients had been randomized.

Because of the protocol amendment, the study became a phase 2 trial. This change added to the primary objective assessment of feasibility for future trial planning—performance of the response-adaptive randomization to select optimal direct oral anticoagulant initiation, and rates of eligibility and enrollment from the lead site, which was the only site required to keep and report screening logs (eFigure in Supplement 2). The study was approved by the institutional review boards at each study site and written informed consent was obtained from the participant or an authorized representative prior to randomization.

The randomized allocation of patients involved an innovative adaptive design, which included response-adaptive randomization based on time to initiate treatment and modeling

Box. Inclusion and Exclusion Criteria

**Inclusion Criteria**

- Had new disabling neurological deficit attributable to new ischemic stroke.
- The minimum lesion diameter was 1.5 cm on screening with computed tomography or magnetic resonance imaging that was performed less than 48 h from stroke onset (time last known well).
- If a lesion was not visible on imaging scan, patient had a National Institutes of Health Stroke Scale score greater than 4.
- If treated with thrombolytic or endovascular therapy for current stroke, the qualifying scan was performed after treatment to rule out clinically significant hemorrhagic transformation.
- Had nonvalvular atrial fibrillation (paroxysmal, persistent, or permanent).
- Were not being treated (or will not be treated) with anticoagulants prior to starting treatment with a direct oral anticoagulant at the randomized time of initiation (except for as prophylaxis against deep vein thrombosis).
- Treating physician planned to treat patient with a direct oral anticoagulant that had been approved by the US Food and Drug Administration.
- Were available to be randomized and begin treatment within 96 h from symptom onset (time last known well), which is the end of the time window for treatment group 1.
- Written informed consent was obtained from the patient or a legally authorized representative.

**Exclusion Criteria**

- Had clinical or imaging evidence of spontaneous intracranial hemorrhage within previous 6 mo. If patients had hemorrhagic transformation of current or previous ischemic stroke or with chronic microbleeding, they could be included per the judgment of the investigators.
- Estimated infarct volume was greater than 50% of middle cerebral artery territory on qualifying scan.
- If the full extent of the lesion was not visible, patient had a National Institutes of Health Stroke Scale score greater than 23.
- Had anticipated need for major surgery over the next 30 d that would require delay, discontinuation of, or extended suspension of anticoagulant treatment for longer than 5 d.
- Symptomatic cerebral edema was expected based on the size and location of ischemic stroke.
- Had current decreased level of consciousness or it was anticipated.
- Had life expectancy of less than 90 d.
- Follow-up for 90 d (in person or by telephone) was not feasible.

of the ischemic and hemorrhagic outcome events. The ischemic and hemorrhagic events were combined within a composite primary end point, but were modeled separately using a monotonic property that assumed the risk of an event increases (ischemic) or decreases (hemorrhagic) as the time to treatment interval lengthens. Response-adaptive randomization was used to independently allocate patients to the 4 groups.

The first 100 patients were enrolled and randomized in a 1:1:1:1 ratio for each cohort, after which the allocation ratios were adjusted based on the primary outcome event data. The allocation ratios were adjusted again based on the primary outcome event data for the first 150 patients. Posterior probabilities were used to estimate which timing groups were optimal for treatment initiation and were recalculated. The randomization allocations were adjusted to favor the groups with higher probabilities.

The randomization allocation was programmed into a secure website (Research Electronic Data Capture; REDCap) that investigators accessed to enroll and randomize patients; REDCap is compliant with the Health Insurance Portability and Accountability Act. Participants, caregivers, and investigators were not blind to randomization.

## Primary Outcome

The composite primary outcome was an ischemic (symptomatic ischemic stroke or systemic embolism as evidenced by either computed tomography or magnetic resonance imaging) or hemorrhagic (symptomatic hemorrhagic transformation of the index ischemic stroke, other symptomatic intracranial hemorrhage, or major systemic hemorrhage) event observed within 30 days from the index stroke time of onset.

Symptomatic intracranial hemorrhage was determined according to each local site definition. Major extracranial hemorrhage was defined according to the criteria of the International Society on Thrombosis and Haemostasis.[9] Outcome events were identified by study personnel either in the hospital or via a follow-up telephone call to the participant or their caregiver at 30 days (±3 days). Participants who had more than 1 primary outcome event documented were categorized according to the first event that occurred. Events were adjudicated by the medical monitor, who was blind to randomization and whether the patients were receiving a direct oral anticoagulant or another antithrombotic medicine at the time of the outcome event.

## Secondary Outcomes

The secondary measures were outcome events by day 90 (the events were adjudicated as described above for the primary outcome), all-cause mortality, and the modified Rankin Scale score at 30 and 90 days. The denominator in reporting adjudicated outcome events and mortality by day 90 are all patients who had nonmissing values at the assessment at day 30 or day 90.

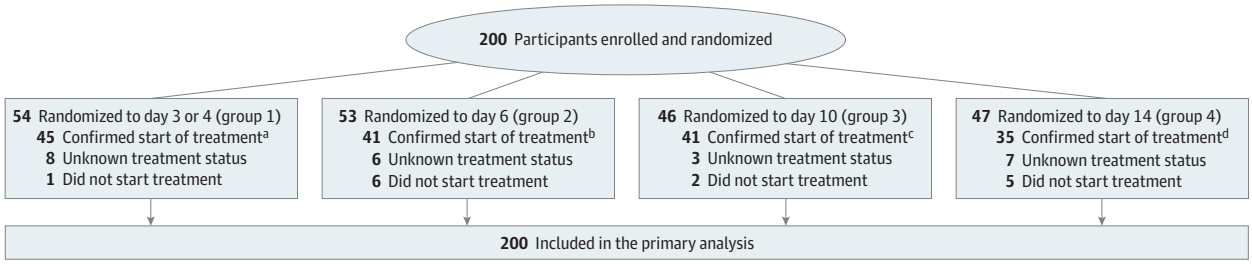
## Data and Safety Monitoring and Adjudication

A physician who was actively engaged in stroke care, but not a part of the research team, monitored the trial for safety and adjudicated outcome events. The monitor, who was blind to both participant randomization assignment and whether the participant was receiving a direct oral anticoagulant at the time of the event, adjudicated the 30- and 90-day outcome events, which were identified by the unblinded investigators who reviewed appropriately redacted hospital notes and imaging reports. The monitor also assigned severity level to the adjudicated events and had the authority to pause study enrollment and request an ad hoc analysis if a concerning number of severe or fatal events occurred. No pauses of study enrollment were requested by the monitor.

## Statistical Analysis

The primary analysis for the trial used posterior probability to assess the optimal delay time to initiate secondary prevention with a direct oral anticoagulant. For the primary intention-

Figure. Participants in a Trial of Optimal Delay Time After Ischemic Stroke to Initiate Anticoagulation




The screening logs of eligible patients and the reasons for exclusion were not required and are not reported except for the lead site (eFigure in Supplement 2).

[a]Of the 45 patients, 37 started within the group-specific treatment window (48-96 hours) and 2 started within 24 hours of the treatment window.

[b]Of the 41 patients, 30 started within the group-specific treatment window (120-144 hours) and 7 started within 24 hours of the treatment window.

[c]Of the 41 patients, 28 started within the group-specific treatment window (216-240 hours) and 6 started within 24 hours of the treatment window.

[d]Of the 35 patients, 19 started within the group-specific treatment window (312-336 hours) and 10 started within 24 hours of the treatment window.

to-treat analysis, patients were analyzed according to the randomization assignment; missing 30-day outcome values were assigned a value of no outcome event.

The posterior probabilities calculated for randomization and the primary analysis were based on a utility score, which combined the estimated event rates for ischemic and hemorrhagic events. The group-specific utility score was defined as the negative sum of the ischemic and hemorrhagic event rates. Higher utility scores correspond to the group with more optimal timing, reflecting the combination of both event rates. These event rates were modeled separately using bayesian statistical approaches.

The log odds of the ischemic event rate were modeled using a sigmoidal model with weakly informative priors, while the log odds of the hemorrhagic event rate were modeled using a normal dynamic linear model. For the normal dynamic linear model, a weakly informative prior was used in group 1, and a prior based on the estimate of the response from the preceding group was used in groups 2 through 4. Thus, the outcomes in the adjacent groups informed the other groups. Bayesian 95% credible intervals were used for the estimates of all event rates and utility scores.

The unit-free utility score drove the randomization probabilities and the final trial success criterion. At the end of the trial, the posterior probability that a group had the optimal time for treatment initiation was calculated based on the utility scores derived from the ischemic and hemorrhagic event rates. The trial goal was to determine if one of the trial groups was superior based on the utility score.

A group would be selected as having optimal timing for treatment initiation if

$$\text{Probability}(\text{group } d \text{ is optimal based on utility score}) > 0.75$$

We intend to separately report a secondary analysis of each event type. The baseline characteristics and secondary outcomes were tabulated and reported as descriptive statistics.

All response-adaptive randomization and primary outcome analyses were performed using the Fixed and Adaptive Clinical Trial Simulator version 7.0 (Berry Consultants)[10] and R version 4.3.2 (R Foundation for Statistical Computing).

To make comparisons across groups, the Kruskal-Wallis rank sum test, the Pearson $\chi^2$ test, and the Fisher exact test were used as appropriate. An adjusted $P<.05$ (for multiple comparisons) was considered significant.

## Results

Between June 22, 2017, and June 2, 2023, 200 patients were randomized (median age, 75 years [IQR, 65-81 years]; 50% were female; 17.5% were Asian, Black, or >1 race; 16.5% were Hispanic; median NIHSS score at presentation, 6.5 [IQR, 4-14]; and median lesion diameter, 3.1 cm [IQR, 2.0-4.4 cm] at the time of randomization). Details on eligibility and enrollment from the screening logs at the lead site appear in the eFigure in Supplement 2. Of 613 hospital admissions with ischemic stroke and AF, 21.5% were eligible and 15.8% were enrolled. The most common reasons for exclusion were insufficient lesion size, no intention by treating physician to begin treatment with a direct oral anticoagulant, and life expectancy less than 90 days. There were no major baseline differences among the groups (**Table 1**). Apixaban was the direct oral anticoagulant prescribed to 89% of the patients.

For the first 100 participants, the probability of randomization into each group was designed as 0.25. After 100 participants had a response for the primary outcome, the posterior probability of being randomized was updated to 0.31 for group 1, 0.28 for group 2, 0.21 for group 3, and 0.20 for group 4. After 150 participants had a response for the primary outcome, the posterior probability of being randomized was updated to 0.27 for group 1, 0.29 for group 2, 0.22 for group 3, and 0.22 for group 4. The resulting sample size for each group was 54 for group 1, 53 for group 2, 46 for group 3, and 47 for group 4 (Table 1).

A primary outcome event by day 30 was observed in 10 participants (5%); there were 7 ischemic events (all stroke) and 3 hemorrhagic events (2 intracranial and 1 systemic). In the primary outcome analysis, the posterior probability was 0.41 that group 1 had the optimal delay time for treatment initiation based on the utility function; the posterior probability was 0.26 for group 2, 0.17 for group 3, and 0.15 for group 4 (**Table 2**). Based only on the

Table 1. Participant Characteristics

| Characteristic | Total (N = 200) | Group 1 (n = 54) | Group 2 (n = 53) | Group 3 (n = 46) | Group 4 (n = 47) | *P* value | |
|---|---|---|---|---|---|---|---|
| | | | | | | Unadjusted[a] | Adjusted[b] |
| Age, median (IQR), y | 75 (65-81) | 76 (67-81) | 71 (63-80) | 73 (64-84) | 78 (67-84) | .23 | .50 |
| Sex, No. (%) | | | | | | | |
| Male | 100 (50) | 22 (41) | 31 (58) | 22 (48) | 25 (53) | .30 | .56 |
| Female | 100 (50) | 32 (59) | 22 (42) | 24 (52) | 22 (47) | | |
| Race, No. (%) | | | | | | | |
| Asian | 8 (4.0) | 4 (7.4) | 2 (3.8) | 0 | 2 (4.3) | .39 | .58 |
| Black | 26 (13.0) | 7 (13.0) | 9 (17.0) | 3 (6.5) | 7 (15.0) | | |
| >1 | 1 (0.5) | 0 | 1 (1.9) | 0 | 0 | | |
| White | 160 (80) | 43 (80) | 40 (75) | 41 (89) | 36 (77) | | |
| Unknown or not reported | 5 (2.5) | 0 | 1 (1.9) | 2 (4.3) | 2 (4.3) | | |
| Hispanic ethnicity, No. (%) | 33 (17.0) | 9 (17.0) | 4 (7.5) | 13 (28.0) | 7 (15.0) | .12 | .35 |
| Score, median (IQR) | | | | | | | |
| Modified Rankin Scale[c] | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0 (0-1) | .36 | .58 |
| NIHSS[d] | 7 (4-14) | 8 (4-14) | 6 (5-15) | 6 (4-14) | 8 (4-13) | .98 | .98 |
| $CHA_2DS_2$-VASc[e] | 5 (4-6) | 5 (5-6) | 5 (4-6) | 5 (4-6) | 6 (5-7) | .02 | .14 |
| Lesion diameter, median (IQR), cm | 3.0 (2.0-4.3) | 3.7 (2.0-5.0) | 3.0 (2.1-3.9) | 3.1 (2.0-4.4) | 3.0 (2.3-3.8) | .56 | .61 |
| Acute reperfusion treatment, No. (%) | | | | | | | |
| Thrombolytic | 76 (38) | 14 (26) | 22 (42) | 24 (52) | 16 (34) | .05 | .21 |
| Mechanical thrombectomy | 65 (33) | 17 (31) | 21 (40) | 15 (33) | 12 (26) | .51 | .61 |
| Prescribed apixaban, No. (%) | 178 (89) | 46 (85) | 48 (91) | 43 (93) | 41 (87) | .57 | .61 |
| Started direct oral anticoagulant, No./total (%) | | | | | | | |
| On time | 162/176 (92) | 45/46 (98) | 41/47 (87) | 41/43 (95) | 35/40 (88) | .14 | .35 |
| >1 d Early | 11/160 (6.9) | 0/44 | 2/40 (5.0) | 5/41 (12.0) | 4/35 (11.0) | .06 | .21 |
| >1 d Late | 10/160 (6.3) | 5/44 (11.0) | 1/40 (2.5) | 2/41 (4.9) | 2/35 (5.7) | .44 | .60 |

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

[a] The Kruskal-Wallis rank sum test, the Pearson $\chi^2$ test, or the Fisher exact test was used to calculate the *P* value.

[b] Adjusted for multiple comparisons and for multiple testing (false discovery rate correction) using the Benjamini-Hochberg method.

[c] Before the current stroke occurred.

[d] Ranges from 0 to 42; higher scores indicate greater neurological deficits.

[e] Ranges from 0 to 9; higher scores indicate a greater risk of stroke.

ischemic event rate, the posterior probability was greater than 0.99 that group 1 had the optimal time for treatment initiation and was less than 0.01 for groups 2 through 4. Based only on the hemorrhagic event rate, the posterior probability was 0.12 that group 1 had the optimal time for treatment initiation; the posterior probability was 0.15 for group 2, 0.19 for group 3, and 0.54 for group 4 (Table 2). The observed and expected event rates in each group by event type appear in **Table 3**. No patients randomized to group 1 had an ischemic event and no patients randomized to group 4 had a hemorrhagic event.

The primary and secondary outcomes by day 30 and day 90 are for nonmissing outcomes and appear in the eTable in Supplement 2. The 30-day outcomes were missing for 20 participants (19 could not be contacted and 1 withdrew consent for further data collection). The 90-day outcomes were missing for 28 participants (3 of whom withdrew consent for further data collection). Day 90 outcome event assessments were obtained for 4 patients with missing data at day 30. The overall 30-day all-cause mortality was 3.3% (6/180) and was 2.0% (1/49) in group 1, 4.3% (2/47) in group 2, 2.3% (1/43) in group 3, and 4.9% (2/41) in group 4. The overall 90-day all-cause mortality was 6.0% (11/184) and was 4.0% (2/50) in group 1, 10.0% (5/48) in group 2, 2.3% (1/44) in group 3, and 7.1% (3/42) in group 4. The median modified Rankin Scale score was 2 (IQR, 1-3) at both 30 and 90 days.

Table 2. Primary and Secondary Analysis for Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation

| | Posterior probability of optimal delay time | | | |
|---|---|---|---|---|
| | Group 1 (day 3 or 4) | Group 2 (day 6) | Group 3 (day 10) | Group 4 (day 14) |
| **Primary analysis** | | | | |
| Based on utility function | 0.41 | 0.26 | 0.17 | 0.15 |
| **Secondary analyses** | | | | |
| Based on ischemic event rate | >0.99 | <0.01 | <0.01 | <0.01 |
| Based on hemorrhagic event rate | 0.12 | 0.15 | 0.19 | 0.54 |

## Discussion

The current trial aimed to determine whether there was an optimal delay time to initiate secondary prevention with a direct

Table 3. Observed and Expected Event Rates and Utility Scores at 30 Days

| | Group 1 (day 3 or 4) | Group 2 (day 6) | Group 3 (day 10) | Group 4 (day 14) |
|---|---|---|---|---|
| No. of participants | 54 | 53 | 46 | 47 |
| Ischemic event | | | | |
| No. of events (%) | 0 | 3 (5.7) | 2 (4.3) | 2 (4.3) |
| Expected event rate, % (95% CI)[a] | 2.8 (1.0 to 5.6) | 3.2 (1.3 to 6.0) | 3.9 (1.6 to 7.3) | 5.3 (2.0 to 10.9) |
| Hemorrhagic event | | | | |
| No. of events (%) | 1 (1.9) | 1 (1.9) | 1 (2.2) | 0 |
| Expected event rate, % (95% CI)[a] | 2.4 (0.7 to 5.9) | 2.0 (0.4 to 5.0) | 1.8 (0.3 to 4.7) | 1.5 (<0.1 to 4.3) |
| Utility score, mean (SD)[b] | −0.053 (0.018) | −0.052 (0.017) | −0.057 (0.019) | −0.067 (0.026) |

[a] Derived from the mean of the posterior distribution.

[b] Negative sum of the ischemic and hemorrhagic event rate; higher scores indicate the groups with more optimal timing.

oral anticoagulant in patients with acute ischemic stroke using a novel application of bayesian response-adaptive randomization. The trial included patients with mild to moderate severity ischemic stroke associated with nonvalvular AF who were within the first 2 weeks of stroke onset.

The results from the primary analysis for the composite outcome of ischemic or hemorrhagic events by day 30 did not identify an optimal timing group for initiation of a direct oral anticoagulant as secondary stroke prevention. However, the posterior probabilities suggest that initiating a direct oral anticoagulant earlier may be better than at later times within the first 2 weeks after stroke onset. An exploratory analysis demonstrated that for prevention of ischemic events by day 30, there was a posterior probability greater than 0.99 that starting use of a direct oral anticoagulant at 3 to 4 days after stroke onset was superior to starting on a later starting day.

With the adoption of direct oral anticoagulants as the preferred antithrombotic therapy to prevent stroke due to AF, the usual practices and concepts of delaying the start of anticoagulation that evolved from the use of heparins and warfarin has come under reconsideration. Randomized trials comparing direct oral anticoagulants vs warfarin for stroke prevention demonstrated fewer bleeding complications with use of a direct oral anticoagulant, but treatment was not initiated within 2 weeks of an ischemic stroke.

In real-world practice, nonadherence is a concern if the recommended start date of anticoagulation treatment is after hospital discharge; therefore, demonstration that early initiation of a direct oral anticoagulant is at least noninferior would support initiating use while patients are still in the hospital. Three recent European randomized clinical trials[11-14] on initiation time for use of a direct oral anticoagulant have addressed this question. The TIMING registry-based trial[11] found that early initiation (±4 days) was noninferior to delayed initiation (5-10 days) for use of a direct oral anticoagulant after acute ischemic stroke in 888 patients (median NIHSS score of 4) for events at 90 days, with numerically lower rates of ischemic stroke and death and no cases of symptomatic intracerebral hemorrhage. The ELAN trial[12] included 2013 participants (median NIHSS score of 3) and found the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days ranged from 2.8% lower to 0.5% higher with early vs later use of direct oral anticoagulants. The trial varied the definition of early and later based on severity of the index stroke. Early initiation was within 48 hours for mild to moderate stroke; later initiation ranged from 3 to 14 days depending on stroke severity. A post hoc analysis[13] of the ELAN trial found no correlation between infarct size and risk of hemorrhagic conversion, which had been the rationale for defining early and later initiation differently for mild to moderate stroke vs severe stroke. The OPTIMAS trial[14] randomized 3621 participants (median NIHSS score of 4) to early initiation (≤4 days) vs delayed initiation (7-14 days) for use of a direct oral anticoagulant and reported noninferiority of events at 90 days with early initiation. These studies[11-14] indicated that earlier initiation is noninferior and may be more favorable than later initiation for rates of ischemic and hemorrhagic events, although the samples were biased toward milder strokes and have not provided evidence of a more specific start day that optimizes the risk trade-off between ischemic and hemorrhagic events.

The current study is the first randomized clinical trial including US patients with AF-related ischemic stroke assessing when to initiate a direct oral anticoagulant, and the first to apply a response-adaptive randomization strategy to the question of delay to initiate a treatment. The included US population had a higher median NIHSS score than the median score in the European trials,[11-14] and went beyond the simple dichotomy of early vs late categories to investigate whether one day was superior to other days within the guideline-recommended 2 weeks after stroke onset. The results regarding the optimal day to begin treatment were inconclusive, but may inform the design of future, larger trials to identify a superior day to initiate use of a direct oral anticoagulant within the early period after stroke onset.

## Limitations

There were limitations to this study. First, the event rate was half that assumed during the planning of the trial. The low number of events and the reduction of sample size from the original trial protocol substantially limited the power to demonstrate an optimal time for treatment initiation.

Second, the study emulated real-world clinical practice, but this approach limited investigation of the relationship between time to initiate a direct oral anticoagulant and the risk of ischemic or hemorrhagic events. Physicians may prescribe a direct oral anticoagulant to be started after hospital discharge,

but whether the medicine is initiated at the intended dose and time is unknown.

Third, study personnel did not attempt to contact participants to ensure adherence with initiation of a direct oral anticoagulant as prescribed and randomized or monitor sites to confirm self-reported information from the 30- and 90-day telephone visits. This pragmatic approach may have contributed to the high rate of patients lost to follow-up, and may have resulted in a substantial number who did not start a direct oral anticoagulant on the prescribed day. However, we were evaluating the strategy of which day to recommend initiation of a direct oral anticoagulant rather than adherence with the recommendations.

Fourth, the slower than expected enrollment despite ischemic stroke being a common disease, the relatively few exclusions, and the few protocol requirements outside standard of care suggests that sites treated eligible patients outside the trial because of physician preference or lack of interest or resources to enroll patients, which would be a potential source of bias.

## Conclusions

A clearly superior day to initiate use of a direct oral anticoagulant for secondary stroke prevention in patients with AF was not identified, but the evidence from this study and multiple larger randomized trials suggests that initiating use of a direct oral anticoagulant earlier is better than at later times within the first 2 weeks after stroke onset.

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*Concept and design:* Warach, Davis, Lawrence, Wick, Savitz, Goldberg, Cruz-Flores, King, Dula, Milling.
*Acquisition, analysis, or interpretation of data:* Warach, Davis, Lawrence, Gajewski, Wick, Shi, Shang, Olson, Prasad, Birnbaum, Richardson, Savitz, Goldberg, Alba, Anderson, Kimmel, Venkatasubba Rao, King, Dula, Milling.
*Drafting of the manuscript:* Warach, Davis, Lawrence, Gajewski, Shi, Anderson, Kimmel, Milling.
*Critical review of the manuscript for important intellectual content:* Davis, Lawrence, Gajewski, Wick, Shi, Shang, Olson, Prasad, Birnbaum, Richardson, Savitz, Goldberg, Cruz-Flores, Alba, Kimmel, Venkatasubba Rao, King, Dula, Milling.
*Statistical analysis:* Lawrence, Gajewski, Wick, Shi, King, Dula, Milling.
*Obtained funding:* Warach, Goldberg, Anderson, Milling.
*Administrative, technical, or material support:* Davis, Lawrence, Olson, Prasad, Richardson, Savitz, Goldberg, Alba, Kimmel, Venkatasubba Rao, Dula, Milling.
*Supervision:* Warach, Davis, Lawrence, Shang, Olson, Prasad, Goldberg, Alba, Kimmel, Milling.

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### REFERENCES

1. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236. doi:10.1161/STR.0000000000000024

2. 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. doi:10.1161/STR.0000000000000375

3. Sacco RL, Adams R, Albers G, et al; American Heart Association; American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(2):577-617. doi:10.1161/01.STR.0000199147.30016.74

4. Seiffge DJ, Werring DJ, Paciaroni M, et al. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol*. 2019;18(1):117-126. doi:10.1016/S1474-4422(18)30356-9

5. 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(9921):955-962. doi:10.1016/S0140-6736(13)62343-0

6. Palaiodimou L, Stefanou MI, Katsanos AH, et al. Early anticoagulation in patients with acute ischemic stroke due to atrial fibrillation: a systematic review and meta-analysis. *J Clin Med*. 2022;11(17):4981. doi:10.3390/jcm11174981

7. Berry SMCB, Lee JJ, Muller P. *Bayesian Adaptive Methods for Clinical Trials*. CRC Press; 2011.

8. King BT, Lawrence PD, Milling TJ, Warach SJ. Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START): methodology of a pragmatic, response-adaptive, prospective randomized clinical trial. *Int J Stroke*. 2019;14(9):977-982. doi:10.1177/1747493019870651

9. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694. doi:10.1111/j.1538-7836.2005.01204.x

10. Berry Consultants, LLC. Fixed and Adaptive Clinical Trial Simulator (FACTS): computer program. Accessed February 19, 2025. https://www.berryconsultants.com/software/facts/

11. Oldgren J, Åsberg S, Hijazi Z, Wester P, Bertilsson M, Norrving B; National TIMING Collaborators. 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(14):1056-1066. doi:10.1161/CIRCULATIONAHA.122.060666

12. Fischer U, Koga M, Strbian D, et al; ELAN Investigators. Early versus later anticoagulation for stroke with atrial fibrillation. *N Engl J Med*. 2023;388(26):2411-2421. doi:10.1056/NEJMoa2303048

13. Goeldlin MB, Hakim A, Branca M, et al; ELAN Investigators. Early vs late anticoagulation in minor, moderate, and major ischemic stroke with atrial fibrillation: post hoc analysis of the ELAN randomized clinical trial. *JAMA Neurol*. 2024;81(7):693-702. doi:10.1001/jamaneurol.2024.1450

14. Werring DJ, Dehbi HM, Ahmed N, et al; OPTIMAS Investigators. Optimal timing of anticoagulation after acute ischaemic stroke with atrial fibrillation (OPTIMAS): a multicentre, blinded-endpoint, phase 4, randomised controlled trial. *Lancet*. 2024;404(10464):1731-1741. doi:10.1016/S0140-6736(24)02197-4