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Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START): Methodology of a pragmatic, response-adaptive, prospective randomized clinical trial

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Abstract

Rationale: An estimated 15% of all strokes are associated with untreated atrial fibrillation. Long-term secondary stroke prevention in atrial fibrillation is anticoagulation, increasingly with non-vitamin K oral anticoagulants. The optimal time to initiate anticoagulation following an atrial fibrillation-related stroke that balances hemorrhagic conversion with recurrent stroke is not yet known.

Aims: To determine if there is an optimal delay time to initiate anticoagulation after atrial fibrillation-related stroke that optimizes the composite outcome of hemorrhagic conversion and recurrent ischemic stroke.

Sample size estimates: The study will enroll 1500 total subjects split between a mild to moderate stroke cohort (1000) and a severe stroke cohort (500).

Methods and design: This study is a multi-center, prospective, randomized, pragmatic, adaptive trial that randomizes subjects to four arms of time to start of anticoagulation. The four arms for mild to moderate stroke are: Day 3, Day 6, Day 10, and Day 14. The time intervals for severe stroke are: Day 6, Day 10, Day 14, and Day 21. Allocation involves a response adaptive randomization via interim analyses to favor the arms that have a better risk–benefit profile.

Study outcomes: The primary outcome event is the composite occurrence of an ischemic or hemorrhagic event within 30 days of the index stroke. Secondary outcomes are also collected at 30 and 90 days.

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Authors' note

The design as described has been approved by the University of Texas at Austin Institutional Review Board to cover the initial phase of the study, launched at four sites within a single hospital network. It has now been approved by six review boards covering 15 hospital sites in Texas through the LSSC. All additional sites included in the trial will be required to obtain approval from their respective institutional review boards.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Discussion: The optimal timing of direct oral anticoagulants post-ischemic stroke requires prospective randomized testing. A pragmatically designed trial with adaptive allocation and randomization to multiple time intervals such as the START trial is best suited to answer this question in order to directly inform current practice on this question.

Keywords

Anticoagulation; stroke risk; stroke prophylaxis; hemorrhagic risk; clinical trial design; response-adaptive randomization

Introduction and rationale

An estimated 13–15% of all strokes are associated with untreated atrial fibrillation (AF), and those patients suffering from stroke and AF typically have larger infarct areas and poorer outcomes.[1,2] Long-term anticoagulation is standard for secondary stroke prevention in patients with AF.[3,4] However, there is a lack of consensus regarding the optimal time to initiate therapy. Current guidelines state that it is reasonable to initiate anticoagulation within 14 days (Class IIa; Level of Evidence B) but do not currently point to a more specific time window.[3] The guidelines also state that it is reasonable to delay initiation of anticoagulation in the presence of high risk for hemorrhagic conversion such as a large infarct or hemorrhagic transformation on initial imaging (Class IIa; Level of Evidence B).[3]

Several observational studies have attempted to clarify this standard by weighing the risks of adverse events following variable initiation of direct oral anticoagulation (DOAC). These studies suggest that early initiation is associated with a low hemorrhage rate and later initiation is associated with increased frequency of recurrent ischemic stroke.[5] To definitively answer this question, four independent, randomized, multi-site trials are already underway. Two of these rely on a dichotomized exposure of early versus late initiation and a third assigning intervals based on severity and imaging features of the index stroke.[5] The START trial is the only one which randomly assigns patients to four distinct time intervals across the current window accepted as standard of care. Randomized clinical trials with pragmatic designs can be more advantageous when studying the real-world effectiveness of low-cost interventions that pose few risks to the subject.[6] Additionally, the START trial applies a response-adaptive randomization (RAR) mechanism which improves upon standard notions of equipoise by responding to the shifting balance in risks identified during the course of the study.[7]

Methods

START is a prospective, multi-center, randomized, response-adaptive, multi-arm time-to-treatment trial. The initial enrollment target is set at 1000 patients with non-valvular AF that have an imaging-confirmed ischemic stroke and an additional cohort of 500 subjects with non-valvular AF-related stroke determined to be at severe risk by their treating physician or otherwise excluded from the mild/moderate cohort for outsized lesion on imaging.

Design

Randomized allocation involves an innovative adaptive design which includes RAR and modeling of the ischemic and hemorrhagic outcome events. Ischemic and hemorrhagic events are combined within a composite primary endpoint, but modeled separately using an assumed monotonic property that the risk of an event increases (ischemic) or decreases (hemorrhagic) as the time-to-treatment interval lengthens.

Patient population

The subject population consists of 1500 total patients with non-valvular AF presenting to the emergency department or neuro-ICU across multiple tertiary-care sites with new neurological deficit attributable to acute ischemic stroke. Ischemic lesions must be at least 15mm in diameter if visible on neuroimaging (if the lesion is not fully visible, a NIHSS≥4 may qualify).

Screening begins when the treating physician makes the determination of intent to treat with a DOAC. Qualifying CT or MR scans must be performed within 48h of symptom onset, but after any thrombolytic or endovascular therapy is performed. Mild-to-moderate risk subjects (n=1000) must not meet any of the following exclusion criteria: evidence of spontaneous intracranial bleeding (sICH) in the previous six months; infarct volume equal to or greater than 50% of the middle cerebral artery (MCA) territory (if lesion is not fully visible, exclude NIHSS≥23); anticipated need to suspend anticoagulation for more than five days within 30 days; or if the patient's life expectancy <90 days.

An additional 500 subjects considered to have high-risk strokes will be enrolled across all sites. Enrollment into the severe arm is based on need for an extended initiation timeline per treating physician or exclusion from the mild-moderate cohort based on prior sICH or lesion volume size in MCA.

Screening and randomization

If a patient appears to be eligible for the study, the research coordinator or investigator approaches the patient or the patient's legally authorized representative (LAR) to recruit them to be in the study, obtain written informed consent, and then consult with the patient's treating physician. Patients must be randomized within 60h of symptom onset (otherwise determined as time of last known well).

RAR is used to allocate subjects to the four time-to-treatment arms independently for each level of risk. The first 100 subjects are equally randomized in a 1:1:1:1 ratio in each cohort, after which allocation ratios are adjusted through interim analyses every 100 enrollments (see Statistical analysis and operating characteristics section).

Intervention

Subjects enrolled in the mild or moderate cohort are randomized to one of four time-to-treatment arms (all±12h): 60, 132, 228, or 324h (i.e. Days 3, 6, 10, or 14). Subjects in the severe risk cohort are randomized to an extended, overlapping set of time-to-treatment arms (all±12h): 132, 228, 324, or 492h (i.e. Days 6, 10, 14, or 21).

Primary outcome—The composite primary outcome event for any patient is the occurrence of any of the following within 30 days of the index stroke: any symptomatic ischemic stroke or systemic embolism as evidenced by either CT or MRI, any symptomatic hemorrhagic transformation of index ischemic stroke, other symptomatic intracranial hemorrhage, or major extracranial hemorrhage.

At the end of the trial, the posterior distribution of the probability that any study arm is the maximally effective arm with regard to the composite outcome will be calculated. If the posterior probability is found to be greater than 0.85 for any one arm, that arm will be selected as statistically the best. Alternatively, if the probability is found to be less than 0.01 for any arm, it will be determined as statistically inferior to the other arms.

Secondary outcomes—Secondary measures are also collected through phone calls at 30 and 90 days from the initial stroke. All-cause mortality at 30 days and event severity will also be considered as secondary outcomes both for testing and data safety monitoring. A recently introduced approach to utility-weighting of clinical events based on the modified Rankin Scale (mRS) will be included in order to integrate the composite event rates with their impact on disability.[8]

Data safety and monitoring

A third-party physician who is actively engaged in stroke care and licensed to practice medicine and is not a part of the research team is used to monitor the safety of patients throughout the START trial. The monitor is available to answer any and all safety questions from participating sites and will review any and all primary outcome events for each subject enrolled in the START trial. The medical monitor will be blinded to the randomized and actual time-to-treatment intervals.

Meetings are held ad hoc to review clinical details of the study outcome events, and the medical monitor provides the study team with adjudication of each event. Secondary outcomes not incorporated into the RAR mechanism, including mortality, will be reviewed for safety concerns as well.

Sample size estimates

The study will enroll 1500 total subjects split between a mild to moderate stroke cohort (n=1000) and a severe stroke cohort (n=500). Simulations of the trial, modeling variations within an average composite outcome rate of 10%[9] under various outcome conditions, confirmed the appropriateness of these sample sizes to detect superior or inferior time-to-treatment arms with high certainty (See Supplemental Material for details).

Statistical analysis and operating characteristics—The design was simulated to determine the trial's operating characteristics separately for the mild/moderate and severe risk cohorts (input and results of mild/moderate cohort simulations presented in Figures 1 and 2; FAST v6.1, Austin, TX). Numerous outcome scenarios were simulated, with five possible modal distributions that could occur in our data presented here:

1. The occurrence of a single superior treatment arm (e.g. Day 14 best).

2. The occurrence of a single inferior treatment arm (e.g. Day 3 worst).
3. No treatment arm being superior or inferior to the others.
4. An inverted-U distribution showing the occurrence of a superior treatment arm (e.g. Day 10 best).
5. The occurrence of two superior treatment arms (e.g. Days 3 and 14 better).

For all scenarios, the RAR allows for improved treatment of the subjects in the trial by placing them on more effective arms. In Scenario 1, the trial has a probability of 0.89 of being able to determine that the longest window is maximally effective. In Scenario 2, the trial has a probability of 0.79 of being able to identify the shortest interval as the worst performing arm.

Operating characteristics for simulations performed using the severe risk group were also tested and reported. These simulations followed patterns similar to the mild/moderate risk cohort and successfully resulted in detection of superior and inferior arms based on the assumptions provided.

Discussion

When comparing multiple FDA-approved treatment strategies against one another, adaptive trials may be highly advantageous.[7,11] By not deviating from standard medical practice except for the randomization of the time to start, the pragmatic design will offer results that can directly advise clinical practice.

Incorporating acquired data into the RAR mechanism also offers multiple ethical benefits,[12] including reducing the number of patients treated with ineffective or inferior treatment timing within the trial.

Currently, screening and enrollment rates are being evaluated concurrent with the active trial, which has provided key insights into trial operation. Funding restrictions limit expansion beyond the current state network. Therefore, study leadership is weighing the option to close the current study at a smaller sample. Available findings would deliver more precise study parameter estimates for relaunch to accrue the planned sample size in an established, nationwide network.

Summary and conclusions

Patients with AF that suffer from a stroke are significantly more likely to have another stroke than the general population. However, the risk of initiating anticoagulation therapy too early could result in a hemorrhagic transformation while starting too late could lead to a recurrent stroke prior to therapy. Most literature on this topic is based on small case series and retrospective analyses that can never fully control for differential misclassification and selection biases.[5,12–14] The optimal timing to initiate DOAC therapy following a stroke requires prospective, randomized testing.[5,15] The START trial seeks to conduct such a study using elements of pragmatic and adaptive trial methods in order to advise clinical practice on the optimal time to initiate anticoagulation in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Simulated primary outcome event rates across five scenarios

Scenario event rates		Arm 1 Day 3	Arm 2 Day 6	Arm 3 Day 10	Arm 4 Day 14
1	Day 14 best				
	Ischemic	0.020	0.020	0.030	0.030
	Hemorrhagic	0.080	0.080	0.080	0.020
	Composite	0.100	0.100	0.110	0.050
2	Day 3 worst				
	Ischemic	0.020	0.020	0.030	0.030
	Hemorrhagic	0.080	0.060	0.040	0.020
	Composite	0.100	0.080	0.070	0.050
3	None				
	Ischemic	0.020	0.040	0.060	0.080
	Hemorrhagic	0.080	0.060	0.040	0.020
	Composite	0.100	0.100	0.100	0.100
4	InvertU-Day 10				
	Ischemic	0.010	0.020	0.030	0.100
	Hemorrhagic	0.120	0.090	0.020	0.010
	Composite	0.130	0.110	0.050	0.110
5	Days 3 and 14 better				
	Ischemic	0.020	0.040	0.060	0.080
	Hemorrhagic	0.080	0.080	0.080	0.020
	Composite	0.100	0.120	0.140	0.100

Note: Theoretical event rates for the occurrence of a recurrent stroke, bleed, and the composite probability are presented for each treatment arm in the five possible scenarios.

Using these estimated possible event rates, 10,000 simulations for each scenario were performed and the average results are summarized in Table 2. Simulations were performed using FACTS (Fixed and Adaptive Clinical Trial Simulator) version 6.1.1.[10]

Table 2.

START trial simulation operating characteristics for trials with 1000 enrollments across five scenarios

Scenario		Arm 1 Day 3	Arm 2 Day 6	Arm 3 Day 10	Arm 4 Day 14	
1	Day 14 best	103.3	142.5	216.1	538.1	*N*
		0	0	0	0.892	*Pr. Max* > 0.85
		0.892	0.739	0.457	0	*Pr. Max* < 0.01
2	Day 3 worst	120.4	176.0	270.9	432.7	*N*
		0	0	0.000	0.398	*Pr. Max* > 0.85
		0.785	0.373	0.020	0.000	*Pr. Max* < 0.01
3	None	233.8	245.8	255.6	264.9	*N*
		0.001	0.001	0.003	0.007	*Pr. Max* > 0.85
		0.072	0.007	0.004	0.074	*Pr. Max* < 0.01
4	InvertU-Day 10	99.8	200.7	480.9	218.7	*N*
		0	0	0.922	0	*Pr. Max* > 0.85
		0.956	0.611	0	0.644	*Pr. Max* < 0.01
5	Days 3 and 14 better	232.8	221.3	217.1	328.8	*N*
		0.004	0	0	0.126	*Pr. Max* > 0.85
		0.072	0.039	0.032	0.016	*Pr. Max* < 0.01

Note: Using event rates for the five possible scenarios, the table summarizes the results of 10,000 simulated trials for each scenario, giving *N*, the average number of subjects enrolled in a treatment arm, and the probability values that a treatment arm is superior or inferior to other treatment arms within each scenario, *Pr. Max* > 0.85 and *Pr. Max* < 0.01, respectively.