Published in final edited form as:

Int J Stroke. 2019 February ; 14(2): 207–214. doi:10.1177/1747493018799981.

The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA) randomized trial: Rationale and Methods

Hooman Kamel, MD[1], **W. T. Longstreth Jr., MD, MPH**[2,3,4], **David L. Tirschwell, MD, MSc**[2], **Richard A. Kronmal, PhD**[5], **Joseph P. Broderick, MD**[6], **Yuko Y. Palesch, PhD**[7], **Caitlyn Meinzer, PhD**[7], **Catherine Dillon, MS**[7], **Irene Ewing, RN, BSN**[6], **Judith A. Spilker, RN, BSN**[6], **Marco R. Di Tullio, MD**[8], **Eldad A. Hod, MD**[9], **Elsayed Z. Soliman, MD, MSc, MS**[10], **Seemant Chaturvedi, MD**[11], **Claudia S. Moy, PhD**[12], **Scott Janis, PhD**[12], **Mitchell S.V. Elkind, MD, MS**[13,14] **ARCADIA Investigators**

[1]Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medical College, New York, NY, USA.

[2]Department of Neurology, University of Washington, Seattle, WA, USA.

[3]Department of Medicine, University of Washington, Seattle, WA, USA.

[4]Department of Epidemiology, University of Washington, Seattle, WA, USA.

[5]Department of Biostatistics, University of Washington, Seattle, WA.

[6]Department of Neurology, University of Cincinnati, Cincinnati, OH, USA.

[7]Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA.

[8]Department of Medicine, Columbia University, New York, NY, USA.

[9]Department of Pathology and Cell Biology, Columbia University, New York, NY, USA.

[10]Epidemiological Cardiology Research Center, Department of Epidemiology and Prevention, and Department of Internal Medicine, Section on Cardiology, Wake Forest School of Medicine, Winston-Salem, NC, USA.

[11]Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA.

[12]National Institutes of Neurological Disease and Stroke, Bethesda, MD, USA.

Corresponding author: Hooman Kamel, MD, Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, 407 East 61st St, New York, NY 10065, Phone: 646-962-8284, hok9010@med.cornell.edu.

Declaration of Conflicting Interests

Dr. Elkind receives compensation for providing consultative services for Abbott, Biotelemetry/Cardionet, Boehringer-Ingelheim, and Sanofi-Regeneron Partnership; receives study medication and laboratory support in kind but no personal compensation from the BMS-Pfizer Alliance for Eliquis® and Roche for the ARCADIA trial; receives royalties from UpToDate for a chapter related to cryptogenic stroke; and serves on the National, Founders Affiliate, and New York City chapter boards of the American Heart Association/American Stroke Association. Dr. Elkind's institution, Columbia University, receives compensation through a service agreement with Medtronic for Dr. Elkind's effort on clinical trials related to cardiac monitoring in stroke patients. No other authors report conflicts of interest.

[13]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA.

[14]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA.

Abstract

Rationale: Recent data suggest that a thrombogenic atrial substrate can cause stroke in the absence of atrial fibrillation. Such an atrial cardiopathy may explain some proportion of cryptogenic strokes.

Aims: The aim of the ARCADIA trial is to test the hypothesis that apixaban is superior to aspirin for the prevention of recurrent stroke in subjects with cryptogenic ischemic stroke and atrial cardiopathy.

Sample Size Estimate: 1,100 participants.

Methods and Design: Biomarker-driven, randomized, double-blind, active-control, phase 3 clinical trial conducted at 120 U.S. centers participating in NIH StrokeNet. *Population Studied:* Patients ≥45 years of age with embolic stroke of undetermined source and evidence of atrial cardiopathy, defined as ≥1 of the following markers: P-wave terminal force >5,000 μV*ms in ECG lead V_1, serum NT-proBNP >250 pg/mL, and left atrial diameter index ≥3 cm/m^2 on echocardiogram. Exclusion criteria include any atrial fibrillation, a definite indication or contraindication to antiplatelet or anticoagulant therapy, or a clinically significant bleeding diathesis. *Intervention:* Apixaban 5 mg twice daily versus aspirin 81 mg once daily. *Analysis*: Survival analysis and the log-rank test will be used to compare treatment groups according to the intention-to-treat principle, including participants who require open-label anticoagulation for newly detected atrial fibrillation.

Study Outcomes: The primary efficacy outcome is recurrent stroke of any type. The primary safety outcomes are symptomatic intracranial hemorrhage and major hemorrhage other than intracranial hemorrhage.

Discussion: ARCADIA is the first trial to test whether anticoagulant therapy reduces stroke recurrence in patients with atrial cardiopathy but no known atrial fibrillation.

One-third of ischemic strokes do not have an identifiable cause.[1] Based on the pattern of brain infarction, these cryptogenic strokes appear to result from distant emboli rather than in-situ arterial occlusion. A widespread consensus supports that these embolic strokes of undetermined source (ESUS) arise from either cardiac structures or large-artery lesions,[2] but such risk factors remain incompletely elucidated. One potential ESUS risk factor is paroxysmal atrial fibrillation/flutter (AF) that existed prior to stroke but remained undiagnosed until after the stroke. However, only a minority of patients with ESUS show any evidence of AF even after several years of continuous heart-rhythm monitoring.[3] Recent evidence indicates that the same atrial pathology that leads to AF may result in thromboembolism even before AF manifests. On a 12-lead electrocardiogram (ECG), the P-wave terminal force in lead V_1 ($PTFV_1$) reflects left atrial abnormalities such as elevated filling pressures, myocyte hypertrophy, fibrosis, and chamber dilatation.[4-6] We have found in

multiple longitudinal cohort studies that $PTFV_1$ is associated with ischemic stroke, particularly cryptogenic and embolic strokes, independent of AF.[7-10] We and others have found associations between left atrial enlargement and ischemic stroke, again independent of AF.[11-14] Amino terminal pro-B-type natriuretic peptide (NT-proBNP), a serum biomarker that partly reflects atrial myocyte dysfunction, has been linked with ischemic stroke independently of AF.[15-17] These findings support the hypothesis that ischemic stroke can arise from a thrombogenic atrial substrate even in the absence of AF. Such an atrial cardiopathy may explain some proportion of ESUS cases. Since AF is currently the sole diagnostic criterion for atrial thrombogenic potential, strokes occurring from left atrial thrombi in the absence of AF may be misclassified as ESUS. Broadening the diagnostic criteria for atrial thromboembolic substrate may allow better recognition of the underlying cause of stroke and may provide a conceptual shift in our understanding of the way in which atrial disease leads to stroke, thus providing a new target for stroke prevention.

Identifying atrial cardiopathy as the cause of stroke may lead to more personalized or individualized therapy for secondary stroke prevention. Antiplatelet drugs are the current standard for antithrombotic therapy in cases of ESUS.[18] However, anticoagulant drugs are substantially more effective than antiplatelet drugs in patients with AF,[19] and given the parallels between atrial cardiopathy and AF, it is likely that anticoagulation will also be superior to aspirin in patients with atrial cardiopathy and no AF. In an analysis of data from the Warfarin-Aspirin Recurrent Stroke Study (WARSS), we found that patients without known AF but with elevated NT-proBNP faced a lower risk of stroke recurrence or death on warfarin than on aspirin.[17] The likelihood of benefit may be even higher with non-vitamin K antagonist oral anticoagulant (NOAC) drugs, which prevent ischemic stroke as well as warfarin but with half the risk of intracranial hemorrhage.[20] Apixaban is a particularly attractive choice because it has a low bleeding risk,[20,21] lowers mortality more than warfarin in patients with AF,[22] and is the only NOAC drug with a Class 1A recommendation in recent AHA/ASA guidelines.[18]

On the other hand, anticoagulation is unlikely to be superior to antiplatelet therapy in ESUS patients without atrial cardiopathy. Many cases of ESUS likely arise from large-artery atherosclerosis that is not currently labeled as a stroke mechanism because it does not result in ≥50% stenosis of the arterial lumen.[23-25] In patients with stroke from known intracranial atherosclerosis, the WASID trial found no benefit of warfarin over aspirin[26] and the SAMMPRIS trial found historically low rates of recurrence with dual antiplatelet therapy.[27] The ARCH trial demonstrated a trend towards fewer recurrent strokes with antiplatelet therapy compared to anticoagulant therapy in those with aortic arch atheroma.[28] These data suggest that anticoagulant agents are unlikely to be superior to antiplatelet therapy in ESUS patients without atrial cardiopathy.

These considerations form the rationale for the AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA) trial, a randomized clinical trial testing the hypothesis that apixaban is superior to aspirin for the prevention of recurrent stroke in patients with ESUS and evidence of atrial cardiopathy.

Methods

Design

ARCADIA is an investigator-initiated, multicenter, biomarker-driven, randomized, double-blind, active-control, phase 3 clinical trial of apixaban versus aspirin in patients who have evidence of atrial cardiopathy and a recent ischemic stroke of unknown cause. 1,100 participants will be recruited over 2.5 years from an estimated 4,400 patients with ESUS screened at 120 sites in the National Institutes of Health (NIH) StrokeNet consortium.[29] Participants are followed for a minimum of 1.5 years and a maximum of 4 years for the primary efficacy outcome of recurrent stroke and the primary safety outcomes of symptomatic intracranial hemorrhage and major hemorrhage other than intracranial hemorrhage. The primary objective of the trial is to test the hypothesis that apixaban is superior to aspirin for the prevention of recurrent stroke in patients with cryptogenic ischemic stroke and atrial cardiopathy. The secondary objective is to test the hypothesis that the relative efficacy of apixaban over aspirin increases with the severity of atrial cardiopathy.

Patient Population

The inclusion criteria are: age ≥45 years, a clinical diagnosis of ischemic stroke that fulfills the definition of ESUS, brain imaging to rule out hemorrhagic stroke, a modified Rankin Scale score ≤4, and the ability to be randomized no later than 120 days after stroke onset (Table 1). ESUS is defined using published consensus criteria (Table 2).[2] To establish ESUS, patients must undergo brain imaging with either computed tomography or magnetic resonance imaging, vascular imaging of the cervical and intracranial cerebral circulation, a 12-lead ECG, transthoracic or transesophageal echocardiography, and ≥24 hours of continuous heart-rhythm monitoring. Additional heart-rhythm monitoring can be performed at the discretion of treating physicians and local investigators, both before and after randomization. A patent foramen ovale is not exclusionary, whether repaired or not.

Key exclusion criteria are: any AF, a definite indication or contraindication to antiplatelet or anticoagulant therapy, a history of spontaneous intracranial hemorrhage, chronic kidney disease with serum creatinine ≥2.5 mg/dL, or a clinically significant bleeding diathesis (Table 1).

Screening and Randomization

Patients who meet all preliminary inclusion and exclusion criteria and provide consent then undergo screening for atrial cardiopathy, defined as ≥1 of the following:

- $PTFV_1$ >5,000 μV*ms on 12-lead ECG;
- Serum NT-proBNP >250 pg/mL;
- Left atrial diameter index ≥3 cm/m^2 on echocardiogram.

The thresholds for each of these biomarkers were chosen based on their associations with increased risk of stroke or stroke recurrence from observational studies. Each was associated with approximately a doubling of risk of stroke in these studies. Although the precise levels of each biomarker that should be used to determine the presence of atrial cardiopathy

remains a matter of study, our use of a broad range of biomarkers and the requirement that only one criterion be met were chosen to facilitate testing of our second hypothesis that atrial cardiopathy represents a spectrum of illness, with different levels of severity.

The left atrial diameter index is determined by the local echocardiography laboratory at each site. $PTFV_1$ is centrally determined at the ARCADIA ECG Core. Serum NT-proBNP is centrally assayed from blood samples sent to the ARCADIA Laboratory Core. Patients who fulfill any one of the atrial cardiopathy criteria are randomized in a 1:1 ratio to apixaban or aspirin using a web-based central randomization system and a randomization method that controls the maximum tolerated imbalance within each NIH StrokeNet Regional Coordinating Center.[30]

Randomization can occur as early as post-stroke day 3, but must be delayed until at least post-stroke day 14 for participants with severe strokes (initial NIH Stroke Scale [NIHSS] score ≥11), hemorrhagic transformation of the index stroke, or uncontrolled hypertension. For all strokes, randomization must occur no later than post-stroke day 120.

Intervention

Participants are randomly assigned to either active apixaban and placebo aspirin, or active aspirin and placebo apixaban. Those assigned to active apixaban receive a standard dose of apixaban 5 mg orally twice daily, except that participants who meet two or more of the standard dose-adjustment criteria (age ≥80 years, weight ≤60 kg, or creatinine ≥1.5 mg/dL) receive apixaban 2.5 mg orally twice daily. Those assigned to active aspirin receive a dose of 81 mg orally once daily. Both study medications must be stopped during any periods when a participant has a definite indication for antiplatelet or anticoagulant therapy, during which time they receive open-label antithrombotic therapy. Participants who are diagnosed with AF after randomization cross over to open-label anticoagulant therapy at the discretion of their treating physicians, and both study medications are discontinued and no longer provided. Study personnel and participants are fully blinded to treatment assignment throughout the trial's duration. In case of an emergency requiring knowledge of a participant's treatment group, for instance life-threatening bleeding, need for emergency surgery, or indication for intravenous thrombolysis for acute ischemic stroke, treating physicians can request emergency unblinding via a 24-hour telephone hotline.

Outcomes

The primary efficacy endpoint is recurrent stroke of any type (ischemic, hemorrhagic, or of undetermined type). The secondary efficacy endpoints are: (a) composite of recurrent ischemic stroke or systemic embolism, and (b) composite of recurrent stroke of any type or death from any cause.

The primary safety outcomes are: (a) symptomatic intracranial hemorrhage, including symptomatic hemorrhagic transformation of an ischemic stroke, and (b) major hemorrhage other than intracranial hemorrhage. The secondary safety outcome is all-cause mortality. All primary and secondary endpoints, except for major hemorrhage, will be adjudicated by two neurologists blinded to treatment assignment. Major hemorrhage will be ascertained by site investigators using the following definition: clinically overt bleeding accompanied by a ≥2

g/dL decrease in the hemoglobin level during a 24-hour period, transfusion of ≥2 units of whole blood or red cells, involvement of a critical non-intracranial site (intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or death.

Exploratory endpoints include: AF, any intracranial hemorrhage, major hemorrhage including any intracranial hemorrhage, symptomatic hemorrhagic transformation of an ischemic stroke, transient ischemic attack, myocardial infarction, minor hemorrhage, systemic embolism, symptomatic deep venous thrombosis, symptomatic pulmonary embolism, ischemic vascular death, and hemorrhagic vascular death.

Data Monitoring Body

Safety oversight will be under the direction of the NIH StrokeNet Data and Safety Monitoring Board (DSMB), which is composed of individuals with the appropriate expertise in overseeing stroke clinical trials. The DSMB will meet at least semi-annually to assess safety data on each arm of the study. The DSMB will review data quality and completeness; monitor fidelity to the study protocol; review the adequacy of participant recruitment and retention; review serious adverse events, clinical outcome events, and adverse events of special interest; and make recommendations to the NIH and the study principal investigators concerning trial continuation, modification, or conclusion.

Sample Size Estimates

The sample size estimation is based on the following assumptions:

- 30-month uniform accrual period and 18-month minimum follow-up period;
- 7% annual risk of recurrent stroke of any type in aspirin-treated participants;
- 40% relative reduction (i.e., hazard ratio of 0.6) in the stroke recurrence rate with apixaban compared to aspirin;
- 3% annual rate of cross-over from blinded aspirin to open-label apixaban because of AF detection;
- 3% annual rate of cross-over from blinded apixaban to open-label aspirin because of bleeding or other adverse events;
- 3.5% annual rate of death in each group;
- 1.5% annual rate of loss to follow-up; and
- one interim analysis for efficacy (or harm) and futility anticipated at the halfway point of the trial.

The assumption of a 7% annual risk of recurrent stroke in aspirin-treated participants was based on a 3.5% annual risk in the overall ESUS population[2] and pilot data indicating a 2-fold higher risk of stroke in those with atrial cardiopathy.[17] The justification for this assumption is that cardioembolic mechanisms of stroke probably have a uniquely high risk of recurrence when treated with only antiplatelet therapy, as seen in our pilot data.[17] The assumed rate of AF detection was calculated based on: (1) survey data from participating

sites indicating that most patients would undergo post-discharge heart-rhythm monitoring before randomization and (2) published rates of AF detection during heart-rhythm monitoring after stroke.[3,31] Expected discontinuation of study drug for reasons other than AF detection or bleeding was implicitly accounted for in the assumed hazard ratio for apixaban.

Given the assumptions above, the study would require a maximum of 1,100 participants in whom 150 recurrent strokes are anticipated. This will provide 80% power to detect the hypothesized hazard ratio for recurrent stroke with apixaban compared to aspirin while allowing for an interim look. An O'Brien-Fleming type Lan-DeMets error spending function[32] will be used for the interim analysis boundaries, assuming a nonbinding futility boundary.

Statistical Analysis

The intention-to-treat principle will be adopted for the analysis of the efficacy outcomes among all randomized participants. Participants who cross over to open-label antithrombotic therapy will continue to be followed for outcomes, and their outcomes will be analyzed according to their original treatment assignment. Safety outcomes will be analyzed in participants who receive at least one dose of study drug. The log-rank statistic will be used to test the null hypothesis, at a two-tailed alpha level of 0.05, that the hazard ratio comparing apixaban to aspirin is 1.

Study Organization and Funding

The ARCADIA trial is being funded by the U.S. National Institute of Neurological Disorders and Stroke of the NIH and will be conducted within StrokeNet. In addition, apixaban, aspirin, and their matching placebo treatments are being provided in kind by the BMS-Pfizer Alliance. Funding for laboratory assay support is being provided by Roche Diagnostics.

Discussion

ARCADIA is the first trial to test whether anticoagulant therapy reduces the occurrence of stroke in patients with atrial cardiopathy but no known AF. The Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) trial (at clinicaltrials.gov) is comparing apixaban to aspirin in patients without a major-risk cardioembolic source but risk factors suggestive of cardiac embolism. This ongoing trial differs from ARCADIA because patients may qualify based on cardiac risk factors other than atrial cardiopathy, such as patent foramen ovale, or based on non-cardiac risk factors such as a high CHA_2DS_2-VASc score; because the outcome is new ischemic lesions on brain imaging rather than clinical stroke; and because it has an open-label design.[33] The strategy of using brain imaging biomarkers to demonstrate the efficacy of a preventive treatment for stroke has not yet been shown to predict clinical efficacy,[34,35] and brain imaging biomarkers are not yet considered a validated surrogate biomarker for stroke. The Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (ESUS) trial (NAVIGATE ESUS) enrolled patients with

ESUS regardless of the presence of atrial cardiopathy.[36] This trial was halted early after an interim analysis involving approximately 7,200 patients found no difference between treatment groups in regards to the primary outcome of stroke or systemic embolism, with no unexpected signals concerning safety. The Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial () is similarly comparing dabigatran to aspirin in patients with ESUS, regardless of atrial cardiopathy. Patients with up to 6 minutes of AF per day are eligible. Given the expected heterogeneity of its patient population—including some patients with nonstenosing plaque, some with atrial cardiopathy and no AF, and some with atrial cardiopathy and brief episodes of AF—the findings of RE-SPECT ESUS will be difficult to extrapolate to patients with atrial cardiopathy but no AF. In this context, the ARCADIA trial is expected to shed light on a biologically distinct stroke mechanism with specific therapeutic implications.

The execution of the ARCADIA trial involves several key challenges. First, the optimal biomarkers of atrial cardiopathy are unknown. The biomarkers used to determine eligibility for randomization in ARCADIA were based on the best available observational data, and thus this trial will serve as an important proof of principle that motivates future work on the ideal characterization of atrial thrombogenic substrate. ARCADIA will include collection of data—including a blood sample repository and central echocardiography and ECG cores—that will permit exploration for additional biomarkers of atrial cardiopathy that may permit even better estimates of risk and therapeutic efficacy with anticoagulation. Second, the trial's power estimation was complicated by secular decreases in recurrent stroke rates in clinical trial participants. To anticipate a continuation of such trends, the sample size calculation for ARCADIA was based on the lower end of current estimates regarding the risk of recurrence after cryptogenic stroke.[2] Furthermore, the reasons for secular decreases in stroke rates, such as greater uptake of statin and antihypertensive therapy, may be less relevant to the specific mechanism of cardiac embolism proposed in this study. Sample size calculations were also complicated by the need for assumptions about rates of cross-over, study drug discontinuation, loss to follow-up, and mortality. All assumptions were based on conservative interpretations of pilot data, but it is possible that actual rates will differ, thus affecting statistical power. Third, the ARCADIA trial targets a specific subpopulation of patients with ischemic stroke, which necessitates screening large numbers of stroke patients to identify eligible participants. The NIH StrokeNet network for ARCADIA, consisting of 120 sites participating with facilitation from 25 Regional Coordinating Centers, will enable this degree of screening. The enrollment of a small subset of the overall ischemic stroke population will limit the generalizability of the trial's findings, but that is by design, since the objective of the trial is to advance precision stroke medicine by isolating a specific underlying stroke mechanism.

Summary and Conclusions

Successful completion of the ARCADIA trial and validation of its primary hypothesis would have implications not only for secondary stroke prevention but primary prevention as well. Any success of anticoagulant therapy in reducing recurrent stroke in this high-risk population with atrial cardiopathy would suggest the possibility of benefit in patients with atrial cardiopathy and no history of stroke. Thus, validation of atrial cardiopathy as a

therapeutic target may set the stage for primary prevention trials. Such trials could feasibly test the benefit of anticoagulant drugs, but may also involve other therapeutic strategies. Validation of the atrial cardiopathy concept would likely lead to a shift away from viewing thromboembolism as mostly the result of blood stasis in a fibrillating atrium and towards viewing it as the result of a complex interplay of left atrial tissue derangements in addition to contractile dysfunction. Such a conceptual shift may spur interest in therapeutic methods—such as specific drugs to ameliorate endothelial dysfunction[37] or a more multimodal approach of aggressive vascular risk factor management to beneficially modify left atrial substrate[38]—that may reduce the risk of left atrial thromboembolism without the bleeding risk that anticoagulant therapy necessarily entails. Therefore, the ARCADIA trial may not only have near-term diagnostic and therapeutic implications for primary and secondary stroke prevention, but also help to spur a conceptual reorientation that will open up many fruitful avenues of future research on reducing the burden of atrial cardiopathy and stroke.

References

1. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke. 2017;48:867–872. [PubMed: 28265016]
2. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429–438. [PubMed: 24646875]
3. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478–2486. [PubMed: 24963567]
4. Alpert MA, Munuswamy K. Electrocardiographic diagnosis of left atrial enlargement. Arch Intern Med. 1989;149:1161–1165. [PubMed: 2524182]
5. Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. Am Heart J. 2001;142:823–827. [PubMed: 11685169]
6. Scott CC, Leier CV, Kilman JW, Vasko JS, Unverferth DV. The effect of left atrial histology and dimension on P wave morphology. J Electrocardiol. 1983;16:363–366. [PubMed: 6227675]
7. Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Electrocardiographic left atrial abnormalities and risk of ischemic stroke. Stroke. 2005;36:2481–2483. [PubMed: 16210557]
8. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr., Nazarian S, et al. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. Stroke. 2014;45:2786–2788. [PubMed: 25052322]
9. Kamel H, Hunter M, Moon YP, Yaghi S, Cheung K, Di Tullio MR, et al. Electrocardiographic left atrial abnormality and risk of stroke: Northern Manhattan Study. Stroke. 2015;46:3208–3212. [PubMed: 26396031]
10. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the Atherosclerosis Risk In Communities study. Ann Neurol. 2015;78:670–678. [PubMed: 26179566]
11. Di Tullio MR, Sacco RL, Sciacca RR, Homma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke. 1999;30:2019–2024. [PubMed: 10512901]
12. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, et al. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. Stroke. 2015;46:1488–1493. [PubMed: 25908460]
13. Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, et al. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. Mayo Clin Proc. 2004;79:1008–1014. [PubMed: 15301328]
14. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation. 1995;92:835–841. [PubMed: 7641364]

15. Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the Atherosclerosis Risk In Communities study. Stroke. 2013;44:961–967. [PubMed: 23471272]
16. Cushman M, Judd SE, Howard VJ, Kissela B, Gutierrez OM, Jenny NS, et al. N-terminal pro-B-type natriuretic peptide and stroke risk: the Reasons for Geographic and Racial Differences in Stroke Cohort. Stroke. 2014;45:1646–1650. [PubMed: 24757103]
17. Longstreth WT Jr., Kronmal RA, Thompson JL, Christenson RH, Levine SR, Gross R, et al. Amino terminal pro-B-type natriuretic peptide, secondary stroke prevention, and choice of antithrombotic therapy. Stroke. 2013;44:714–719. [PubMed: 23339958]
18. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. 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;45:2160–2236. [PubMed: 24788967]
19. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–867. [PubMed: 17577005]
20. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, 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;383:955–962. [PubMed: 24315724]
21. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806–817. [PubMed: 21309657]
22. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–992. [PubMed: 21870978]
23. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. JACC Cardiovasc Imaging. 2012;5:397–405. [PubMed: 22498329]
24. Gupta A, Gialdini G, Lerario MP, Baradaran H, Giambrone A, Navi BB, et al. Magnetic resonance angiography detection of abnormal carotid artery plaque in patients with cryptogenic stroke. J Am Heart Assoc. 2015;4:e002012. [PubMed: 26077590]
25. Gupta A, Gialdini G, Giambrone AE, Lerario MP, Baradaran H, Navi BB, et al. Association between nonstenosing carotid artery plaque on MR angiography and acute ischemic stroke. JACC Cardiovasc Imaging. 2016;9:1228–1229. [PubMed: 26897689]
26. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352:1305–1316. [PubMed: 15800226]
27. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993–1003. [PubMed: 21899409]
28. Amarenco P, Davis S, Jones EF, Cohen AA, Heiss WD, Kaste M, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. Stroke. 2014;45:1248–1257. [PubMed: 24699050]
29. NIH StrokeNet. https://www.nihstrokenet.org/. Accessed November 29, 2017.
30. Zhao W, Hill MD, Palesch Y. Minimal sufficient balance-a new strategy to balance baseline covariates and preserve randomness of treatment allocation. Stat Methods Med Res. 2015;24:989–1002. [PubMed: 22287602]
31. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467–2477. [PubMed: 24963566]
32. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659–663.
33. Geisler T, Poli S, Meisner C, Schreieck J, Zuern CS, Nagele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. Int J Stroke. 2017;12:985–990. [PubMed: 27881833]

34. ten Dam VH, van den Heuvel DM, van Buchem MA, Westendorp RG, Bollen EL, Ford I, et al. Effect of pravastatin on cerebral infarcts and white matter lesions. Neurology. 2005;64:1807–1809. [PubMed: 15911821]

35. O'Donnell MJ, Eikelboom JW, Yusuf S, Diener HC, Hart RG, Smith EE, et al. Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. Am Heart J. 2016;178:145–150. [PubMed: 27502862]

36. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med. 2018

37. Perros F, Ranchoux B, Izikki M, Bentebbal S, Happe C, Antigny F, et al. Nebivolol for improving endothelial dysfunction, pulmonary vascular remodeling, and right heart function in pulmonary hypertension. J Am Coll Cardiol. 2015;65:668–680. [PubMed: 25677428]

38. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64:2222–2231. [PubMed: 25456757]

Table 1.

Inclusion and Exclusion Criteria for the ARCADIA Trial.

Inclusion Criteria:
Age ≥45 years
Clinical diagnosis of ischemic stroke with brain imaging to rule out hemorrhagic stroke
Modified Rankin Scale score ≤4
Ability to be randomized no later than 120 days after stroke onset
Embolic stroke of undetermined source (see Table 2)
Exclusion Criteria:
Atrial fibrillation of any duration prior to randomization
Clear indication for treatment-dose anticoagulant therapy
Left ventricular ejection fraction <30%
Definite indication for antiplatelet agent
History of spontaneous intracranial hemorrhage
Chronic kidney disease with serum creatinine ≥2.5 mg/dL
Active hepatitis or hepatic insufficiency with Child-Pugh score B or C
Pregnancy risk
Known allergy or intolerance to aspirin or apixaban
Concomitant participation in another clinical trial involving a drug or intervention
Any condition that precludes follow-up or safe participation in the trial
Inability to obtain written, informed consent from patient or surrogate for trial participation

Table 2.

Criteria for Embolic Stroke of Undetermined Source.

1. Stroke that is not lacunar:
Lacunar is defined as a subcortical (this includes pons and midbrain) infarct in the distribution of the small, penetrating cerebral arteries whose largest dimension is ≤1.5 cm on CT, ≤2.0 cm on MRI diffusion images, or ≤1.5 cm on MRI T2-weighted images
The following are not considered lacunes: multiple simultaneous small deep infarcts, lateral medullary infarcts, and cerebellar infarcts
Patients with a clinical lacunar stroke syndrome and no infarct on imaging are excluded
2. Stroke that is not due to large-artery atherosclerosis:
Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis of the artery supplying the area of ischemia
Patients must undergo vascular imaging of the extracranial and intracranial vessels using either catheter angiography, CT angiogram, MR angiogram, or ultrasound, as considered appropriate by the treating physician and local principal investigator
3. Stroke that is not due to a major-risk cardioembolic source*:
Atrial fibrillation
Intracardiac thrombus
Mechanical prosthetic heart valve
Atrial myxoma or other cardiac tumor
Mitral stenosis
Myocardial infarction within prior 4 weeks
Left ventricular ejection fraction <30%
Valvular vegetations
Infective endocarditis
4. Stroke that is not due to another specific cause:
Arteritis
Dissection
Migraine
Vasospasm
Drug abuse
Hypercoagulability

* Patent foramen ovale is not exclusionary, whether repaired or not