Stroke

ORIGINAL CONTRIBUTION

Multiterritory Brain Infarcts, Anticoagulation, and Recurrence After Cryptogenic Stroke: A Subgroup Analysis of the ARCADIA Trial

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BACKGROUND: In patients with cryptogenic stroke, the characteristics of multiterritory brain infarcts, the recurrent stroke risk, and the response to anticoagulation remain unclear.

METHODS: The ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) screened patients with cryptogenic stroke for atrial cardiopathy at 185 centers in the United States and Canada from 2018 to 2022. Investigators reported baseline acute brain infarction in the left anterior, right anterior, and posterior circulation. Atrial cardiopathy was defined as P-wave terminal force in ECG lead V1s >5000 μV·ms, NT-proBNP (N-terminal pro-B-type natriuretic peptide) >250 pg/mL, or left atrial diameter index ≥3 cm/m^2. Site echocardiography laboratories determined left atrial diameter index and a central echocardiography laboratory determined LVEF. We used ANCOVA to examine whether atrial cardiopathy biomarkers or LVEF were associated with the number of territories with infarction. Cox regression was used to examine whether the number of infarct territories was associated with recurrent stroke or modified the effect of apixaban compared with aspirin.

RESULTS: Among 3464 patients with reported baseline magnetic resonance imaging data, 220 (6.4%) had no visible acute infarct and 2794 (80.7%) had acute infarction in 1, 374 (10.8%) in 2, and 76 (2.2%) in 3 territories. Atrial cardiopathy biomarkers and LVEF were not associated with the number of infarct territories. Among 937 of these 3464 patients who were randomized, we found higher risks of recurrent stroke associated with infarcts in 2 territories (hazard ratio, 2.4 [95% CI, 1.3–4.2]) or 3 territories (hazard ratio, 3.7 [95% CI, 1.5–9.3]) relative to single-territory infarction, whereas the absence of visible infarction was not associated with recurrence (hazard ratio, 1.8 [95% CI, 0.6–4.9]). The number of infarct territories did not modify the effect of apixaban versus aspirin in relation to recurrent stroke (*P* for interaction, 0.71).

CONCLUSIONS: Multiterritory brain infarction was not associated with atrial cardiopathy biomarkers or LVEF in the ARCADIA trial. Multiterritory infarction was associated with a significantly higher risk of recurrent stroke, but this heightened risk was not reduced by apixaban relative to aspirin.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: apixaban ■ anticoagulant ■ aspirin ■ atrial fibrillation ■ cardiopathies

The ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) found no benefit of apixaban compared with aspirin for secondary stroke prevention in patients with cryptogenic stroke and evidence of atrial cardiopathy.[1] The trial screened all patients with cryptogenic stroke, regardless

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Nonstandard Abbreviations and Acronyms

ARCADIA	Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke
CHANCE	Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events
MRI	Magnetic resonance imaging
NAVIGATE-ESUS	New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial Versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source
NIHSS	National Institutes of Health Stroke Scale
NT-proBNP	N-terminal pro-B-type natriuretic peptide

of the number and location of acute brain infarcts at baseline. Higher numbers of acute brain infarcts at the time of an index stroke have been associated with a higher risk of stroke recurrence.[2,3] In addition, the presence of acute brain infarcts in multiple arterial territories is often considered an imaging signature of cardioembolic stroke.[4] Thus, among patients with cryptogenic stroke, the number of territories with acute brain infarcts may reflect the likelihood of a central embolic source and the risk of recurrent stroke. The baseline characteristics of patients with multiterritory brain infarcts, their recurrent stroke risk, and their response to anticoagulant versus antiplatelet therapy are not well understood. We hypothesized that ARCADIA patients with multiterritory brain infarcts on baseline imaging would be more likely to have an underlying cardioembolic cause and therefore a recurrent stroke risk modifiable by anticoagulation treatment.

METHODS

Design

ARCADIA was a multicenter, randomized clinical trial comparing apixaban to aspirin for the prevention of recurrent stroke in patients with a recent cryptogenic stroke and evidence of atrial cardiopathy. The trial was funded by National Institutes of Health and performed at 185 sites in National Institutes of Health StrokeNet and the Canadian Stroke Consortium. The StrokeNet Central institutional review board and the institutional review boards at all participating sites approved the trial, and all patients provided written, informed consent for trial participation, and analysis of their data. Details of the trial rationale and methodology and the primary results have been published previously.[1,5] The trial data are publicly available to researchers via written request to National Institutes of Health. We followed the STROBE guidelines in reporting this analysis.

Patient Population

Patients ≥45 years old with a cryptogenic ischemic stroke within the prior 180 days were approached for written, informed consent to participate in ARCADIA and undergo biomarker screening for atrial cardiopathy. Cryptogenic stroke was defined as an ischemic stroke that lacked an apparent cause after standard investigation, with a requirement for: (1) computed tomography or magnetic resonance imaging (MRI) of the brain to exclude a lacunar infarct; (2) vascular imaging of the cervical and intracranial arteries to exclude stroke from large-artery atherosclerosis associated with ≥50% luminal stenosis; and (3) transthoracic or transesophageal echocardiography, a 12-lead ECG, and ≥24 hours of continuous heart-rhythm monitoring to exclude a major-risk cardioembolic source including any atrial fibrillation. For this posthoc analysis, we included only the 3464 patients with baseline brain MRI data, who comprised 92.5% of the trial's 3745 enrolled patients.

Intervention

Among patients who consented to participate in ARCADIA and underwent biomarker screening, those who met criteria for atrial cardiopathy and continued to meet all eligibility criteria were randomly assigned in double-blind fashion to apixaban or aspirin. Atrial cardiopathy was defined as the presence of at least one of the following biomarker criteria: P-wave terminal force in ECG lead V_1 ≥5000 μV·ms, serum NT-proBNP (N-terminal pro-B-type natriuretic peptide)>250 pg/mL, or left atrial diameter index ≥3 cm/m^2 on echocardiogram.

Measurements

In all patients who consented for screening, the territory of acute brain infarction was ascertained by site investigators based on standard-of-care imaging and reported via a case report form. The number of arterial territories with acute infarction could range from 0 (no acute infarct seen) to 3 (acute infarcts in the left anterior, right anterior, and posterior circulation). The anterior circulation included the territory of both the middle cerebral artery and the anterior cerebral artery. In 149 patients, the site investigator documented that an acute infarct was seen but did not record the affected territory; we classified these patients as having a single infarcted territory in our primary analysis, but we excluded them in a sensitivity analysis.

Using previously validated methods, the study ECG core centrally determined P-wave terminal force in ECG lead V1. Using the Elecsys assay (Roche Diagnostics, Basel, Switzerland), the study core laboratory centrally measured NT-proBNP. The local echocardiography laboratory at each site determined left atrial diameter index, and the trial's central echocardiography laboratory determined the left ventricular ejection fraction from echocardiogram images transmitted by sites.

The primary efficacy end point was recurrent stroke of any type (ischemic, hemorrhagic, or undetermined type) as adjudicated by 2 neurologists blinded to treatment assignment. Patients were assessed every 3 months and this end point was ascertained from the time of randomization until the trial ended or patients were lost to follow-up, withdrew from the trial, or died.

Covariates included in this analysis were all assessed at the time of consent for trial enrollment and comprised:

demographics (age, sex, race, and ethnicity), index stroke severity (National Institutes of Health Stroke Scale [NIHSS]), risk factors and comorbidities (body mass index, prior stroke or transient ischemic attack, heart failure, coronary artery disease, peripheral artery disease, hypertension, diabetes, active or prior tobacco use, and cancer), basic laboratory assessments (creatinine, hemoglobin, platelet count), and the time from stroke until atrial cardiopathy screening.

Statistical Analyses

We used ANCOVA to compare atrial cardiopathy markers across infarct territory numbers after adjustment for the covariates above. We did not impute missing variables given the low frequency of missingness for predictors and covariates. P-wave terminal force in ECG lead V_1 and left atrial diameter index were modeled as continuous variables, whereas NT-proBNP was log-transformed given its skewed distribution. Among patients randomized to study treatment, Cox regression models were used to examine the association between the number of infarct territories and the risk of recurrent stroke, as well as the interaction between the number of infarct territories and anticoagulation treatment benefit. To explore the role of stroke severity and time since stroke onset, we examined the relationship between atrial cardiopathy biomarkers and the number of infarct territories in patients with moderate-to-severe stroke, defined as an NIHSS score ≥5, and in patients with recent stroke, defined as stroke within 30 days before randomization. In addition, we examined the interaction between the NIHSS score and the effect of apixaban, as well as the interaction between the number of days from stroke onset until randomization and the effect of apixaban, in patients with and without multiterritory infarction.

RESULTS

Baseline Characteristics and Number of Infarct Territories

Of 3745 patients with cryptogenic stroke who provided consent to enroll in the ARCADIA trial, we excluded 281 without baseline MRI data. Among the remaining 3464 patients, 220 (6.4%) had no visible acute infarct and 2794 (80.7%) had acute infarction in 1 arterial territory, 374 (10.8%) in 2 territories, and 76 (2.2%) in all 3 territories. No baseline characteristic was clearly associated with an increasing number of infarct territories except for hypertension, which was increasingly prevalent with higher numbers of baseline infarct territories (Table S1).

Atrial Cardiopathy Biomarkers and Number of Infarct Territories

Distributions of atrial cardiopathy biomarkers among patients with different numbers of infarct territories are shown in Figure 1. We found no significant differences in covariate-adjusted mean atrial cardiopathy biomarker levels across infarct territory numbers (ln [NT-proBNP], P=0.21; P-wave terminal force in ECG lead V_1, P=0.10; left atrial diameter index, P=0.62). We also found no significant difference in the adjusted mean left ventricular ejection fraction across infarct territory numbers (P=0.15).

Number of Infarct Territories, Recurrent Stroke, and Effect of Apixaban

Of the 1015 ARCADIA patients who met atrial cardiopathy biomarker criteria and were randomized, 937 had baseline MRI data, of whom 49 (5.2%) had no acute infarction seen, and 765 (81.6%) had acute infarction in 1 arterial territory, 101 (10.8%) in 2, and 22 (2.4%) in all 3 (Table). Compared with patients with single-territory infarction, those with infarction in 2 territories had an ≈2.5-fold higher risk of recurrent stroke (hazard ratio, 2.4 [95% CI, 1.3–4.2]) and those with infarction in all 3 territories had an ≈3.5-fold higher risk (hazard ratio, 3.7 [95% CI, 1.5–9.3]). Patients with no visible infarction had an increased risk of recurrent stroke which was not significantly different from those with single-territory infarction (hazard ratio, 1.8 [95% CI, 0.6–4.9]). These associations were broadly similar after adjustment for demographics and comorbidities (Figure 2). The number of arterial territories with acute infarction did not modify the effect of apixaban versus aspirin in relation to recurrent stroke in an unadjusted model (P for interaction, 0.71; Figure 3).

Sensitivity Analysis

All of our findings were similar in a sensitivity analysis excluding the 149 patients with missing information on the affected arterial territory.

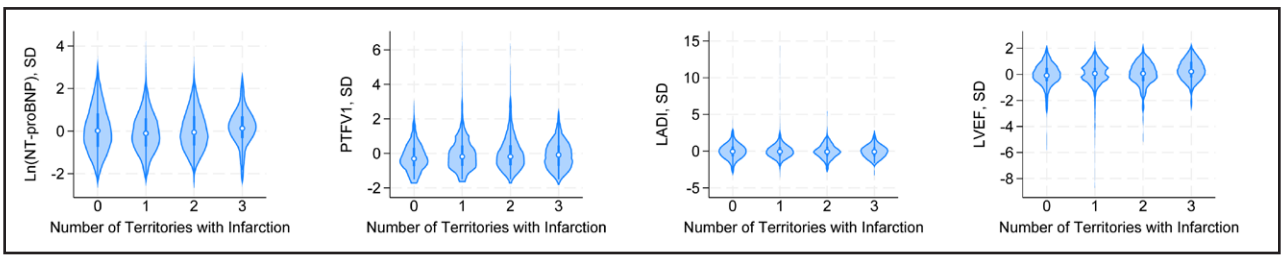

Figure 1. Distribution of atrial cardiopathy biomarkers and left ventricular ejection fraction (LVEF) in the ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke), by number of baseline infarct territories.
LADI indicates left atrial diameter index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and $PTFV_1$, P-wave terminal force in lead V_1.

Table. Characteristics of 937 Randomized ARCADIA Trial Patients with Baseline MRI Data, Stratified by Territories With Acute Brain Infarction

Characteristic	0 Territories (N=49)	1 Territory (N=765)	2 Territories (N=101)	3 Territories (N=22)	*P* value*
Age, mean (SD), y	67.5 (10.0)	67.8 (10.9)	67.6 (11.6)	69.4 (9.9)	0.91
Female	23 (46.9%)	347 (45.4%)	52 (51.5%)	9 (40.9%)	0.66
Race					0.35
White	37 (77.1%)	580 (76.8%)	62 (63.9%)	17 (81.0%)	
Black	9 (18.8%)	159 (21.1%)	32 (33.0%)	4 (19.0%)	
Asian	1 (2.1%)	11 (1.5%)	2 (2.1%)	0 (0.0%)	
Other	1 (2.1%)	5 (0.7%)	1 (1.0%)	0 (0.0%)	
Hispanic or Latino ethnicity	8 (16.7%)	57 (7.5%)	6 (6.1%)	4 (18.2%)	0.03
National Institutes of Health Stroke Scale score, median (IQR)	1 (0–3)	1 (0–3)	2 (0–3)	0 (0–1)	0.12
Body mass index, mean (SD), kg/m^2	31.3 (6.6)	29.6 (6.7)	29.4 (6.5)	29.6 (7.9)	0.31
Laboratory tests					
Creatinine, mg/dL	0.9 (0.3)	1.0 (0.3)	1.0 (0.3)	1.0 (0.5)	0.38
Hemoglobin, g/dL	13.3 (1.7)	13.2 (1.7)	13.1 (1.8)	13.4 (1.4)	0.92
Platelets, per µL	227.7 (67.4)	233.2 (66.0)	225.7 (70.8)	224.2 (65.0)	0.64
Atrial cardiopathy biomarkers					
PTFV$_1$, mean (SD), µV·ms	4087 (2406)	4760 (2657)	5381 (3246)	4077 (2066)	0.02
LA diameter index, mean (SD), cm/m^2	1.9 (0.6)	1.9 (0.5)	1.9 (0.4)	1.8 (0.4)	0.71
NT-proBNP, median (IQR), pg/mL	356 (211–722)	288 (93–524)	324 (129–565)	311 (256–445)	0.08
LV ejection fraction, mean (SD), %	58.2 (8.1)	60.5 (7.5)	60.4 (8.5)	63.3 (5.0)	0.07
Medical comorbidities					
Hypertension	39 (79.6%)	585 (76.5%)	81 (80.2%)	16 (72.7%)	0.77
Prior or current tobacco use	20 (40.8%)	315 (41.2%)	55 (54.5%)	10 (45.5%)	0.09
Diabetes	22 (44.9%)	226 (29.5%)	38 (37.6%)	6 (27.3%)	0.06
Prior stroke or transient ischemic attack	12 (24.5%)	149 (19.5%)	25 (24.8%)	4 (18.2%)	0.54
Cancer	6 (12.2%)	107 (14.0%)	16 (15.8%)	4 (18.2%)	0.88
Coronary artery disease	6 (12.2%)	69 (9.0%)	8 (7.9%)	1 (4.5%)	0.73
Heart failure	4 (8.3%)	50 (6.6%)	9 (8.9%)	1 (4.5%)	0.77
Peripheral artery disease	1 (2.0%)	13 (1.7%)	3 (3.0%)	1 (4.5%)	0.66

ARCADIA indicates Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; IQR, interquartile range; LA, left atrial; LV, left ventricular; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and PTFV$_1$, P-wave terminal force in lead V$_1$.

*Comparisons made using t-tests, Kruskal-Wallis rank tests, and χ^2 tests, as appropriate.

Subgroup Analyses and Tests of Interaction

Atrial cardiopathy biomarkers were not associated with the number of infarct territories in patients with NIHSS score ≥5 (*P*>0.05 for all ANCOVA tests; Figure S1) or patients who were randomized within 30 days of stroke onset (*P*>0.05 for all ANCOVA tests; Figure S2). We found no interaction between the NIHSS score and the effect of apixaban on recurrent stroke in patients with multi-territory infarction at baseline (*P* for interaction, 0.34) or without (*P* for interaction, 0.82). We found no interaction between the number of days from stroke onset until randomization and the effect of apixaban on recurrent stroke in patients with multiterritory infarction at baseline (*P* for interaction, 0.36) or without (*P* for interaction, 0.20).

DISCUSSION

Among patients with cryptogenic stroke, we found no association between biomarkers of atrial cardiopathy and the number of index brain infarct territories. Greater numbers of infarct territories were associated with an increased risk of recurrent stroke but did not modify the effect of apixaban compared with aspirin.

Despite the common belief among neurologists that brain infarction in multiple arterial territories indicates an underlying cardioembolic source, previous studies have reported conflicting findings about whether cardioembolic stroke is more strongly associated with multiterritory brain infarcts than other stroke mechanisms.[4,6–9] In the studies that found no association, a common alternative stroke cause leading to multiterritory infarction

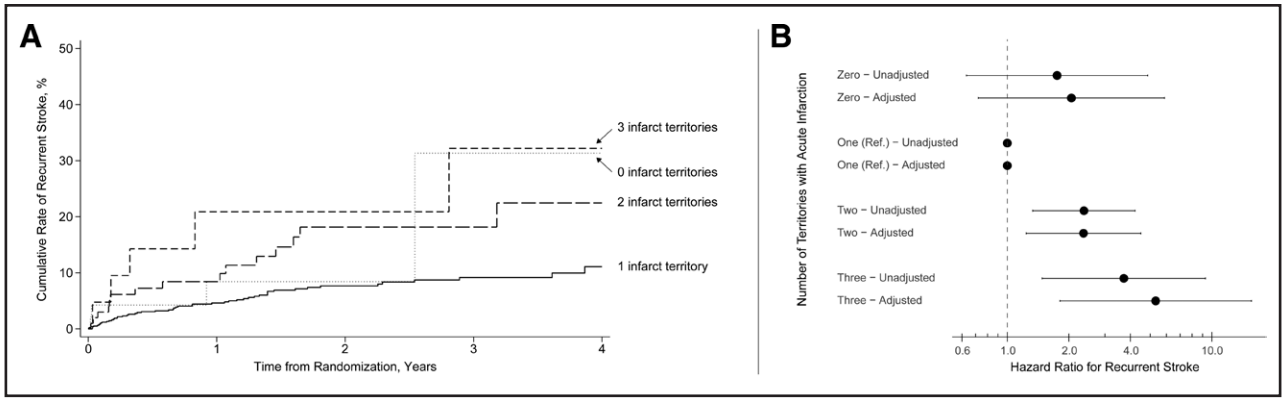

Figure 2. Cumulative rates (A) and hazard ratios (B) for recurrent stroke in the ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke), by number of baseline infarct territories.

was large-artery atherosclerosis—aortic, cervical, or intracranial—often in the setting of anatomic variants such as a fetal posterior cerebral artery.[8] In this context, our findings suggest that multi-territory infarction should not be viewed as a specific sign of an underlying cardioembolic source among patients with an acute cryptogenic stroke. Multiterritory infarcts were not associated with atrial cardiopathy biomarkers, left ventricular ejection fraction, or a benefit from apixaban compared with aspirin. Even the presence of acute infarcts in all 3 territories, sometimes referred to as the triple-territory sign, was not associated with higher levels of atrial cardiopathy biomarkers or lower left ventricular ejection fraction.

Regardless of the cause of multiterritory infarcts, we found that higher numbers of infarct territories at baseline were associated with a higher risk of recurrent stroke. These findings are consistent with prior studies linking the presence of multiterritory infarcts with a higher risk of recurrence after cryptogenic stroke[10,11] or minor ischemic stroke.[2,3] In the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events), participants with multiple infarcts at baseline had a more pronounced benefit from dual antiplatelet therapy than those with a single infarct,[2] whereas no such effect modification was found for anticoagulation in the NAVIGATE-ESUS trial (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial Versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) or in our present analysis of the ARCADIA trial.[11] These findings suggest that multi-territory infarcts should not be interpreted as evidence of a cardioembolic source that will respond to empirical anticoagulation. One hypothesis that may be worth exploring is that multi-territory infarcts may arise from currently undiagnosed atherosclerotic sources,[12] which may not respond to

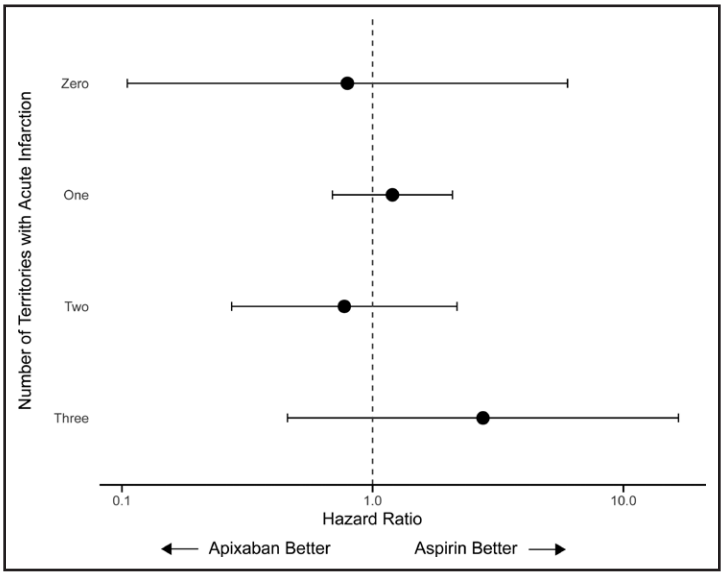

Figure 3. Effect of apixaban vs aspirin on recurrent stroke in the ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke), by number of baseline infarct territories.
P value for interaction, 0.71.

anticoagulant therapy any more than to antiplatelet therapy. The very high rate of recurrence in patients with multiterritory infarcts—>10% at 1 year in our analysis—suggests that this subset of patients with cryptogenic stroke may warrant further study to identify better preventive therapies.

In patients presenting with transient ischemic attack or low-risk transient or minor neurological symptoms, the absence of acute infarction on MRI has been associated with a lower risk of future stroke.[13,14] However, among patients clinically diagnosed with ischemic stroke, the absence of acute infarction at baseline is not associated with a significantly lower risk of stroke over the long term.[15] In the ARCADIA trial, we similarly found that the 6% of patients without visible infarction at baseline were not at an appreciably lower risk of recurrent stroke compared with those with a single visible infarct. These findings underscore that ischemic stroke remains a clinical diagnosis and that MRI-negative strokes do not necessarily have a benign natural history, cautioning against over-reliance on MRI in patients with symptoms or signs of ischemic stroke.

Our study has several limitations. First, we collected limited information from site investigators about baseline imaging. Therefore, we could not perform detailed analyses about the exact number, size, and location of individual infarcts. It is also possible that some infarcts visible on baseline imaging were not reliably reported by sites. Second, we lacked data on the degree and characteristics of nonstenosing atherosclerotic plaque in the aorta and cervical and intracranial large arteries, or on anatomic variants such as a fetal posterior cerebral artery. Third, given relatively small numbers of recurrent strokes, our estimates of treatment effect were relatively imprecise when stratified by the number of infarct territories. Fourth, we were only able to examine treatment effect modification and associations with recurrent stroke among cryptogenic stroke patients who met the atrial cardiopathy biomarker criteria for the trial. However, given the lack of association between these biomarkers and the number of infarct territories, our findings may still be generalizable to cryptogenic stroke patients regardless of atrial cardiopathy. Fifth, we lacked sufficient numbers of events to allow detailed analyses of treatment effect in specific subgroups such as those with higher NIHSS scores or those who were randomized soon after their index stroke.

In summary, multi-territory brain infarcts in the ARCADIA trial were not associated with markers of atrial cardiopathy or left ventricular ejection fraction. The presence of multi-territory infarction was associated with a significantly higher risk of recurrent stroke, but this heightened risk was not reduced by apixaban relative to aspirin.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figures S1 and S2

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