Stroke

ORIGINAL CONTRIBUTION

Apixaban and Recurrent Stroke Risk With Left Ventricular Dysfunction: A Secondary Analysis of the ARCADIA Trial

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BACKGROUND: Major uncertainty remains about the relationship between left ventricular (LV) systolic dysfunction, recurrent stroke, and the optimal antithrombotic therapy for secondary stroke prevention in patients with recent stroke and LV systolic dysfunction.

METHODS: We performed a post hoc analysis of data from the ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke), a randomized trial comparing apixaban versus aspirin for secondary stroke prevention in patients with cryptogenic stroke and atrial cardiopathy. Echocardiograms were sent from 185 enrolling sites in the United States and Canada for central review at the trial echocardiography laboratory. We defined LV systolic dysfunction as LV fractional shortening <25%, LV ejection fraction <50%, or any LV wall motion abnormality. The primary outcome of interest was recurrent ischemic stroke. First, we built Cox proportional hazard models to evaluate the association between LV systolic dysfunction and recurrent ischemic stroke risk adjusted for imbalanced covariates. Next, we used Cox proportional hazard models and interaction terms to compare the effect of apixaban versus aspirin on the outcome of interest in patients with and without LV systolic dysfunction.

RESULTS: Among 964 patients with complete echocardiographic data of the 1015 patients enrolled in the trial, 165 (17.1%) had LV systolic dysfunction (mean age, 67 years; 43% female; mean follow-up, 1.7 years), and 799 (82.9%) had no LV systolic dysfunction (mean age, 68 years; 56% female; mean follow-up, 1.5 years). Recurrent ischemic stroke occurred more frequently in patients with LV systolic dysfunction (n=15, 9.1%) compared with those without LV systolic dysfunction (n=50, 6.3%), but LV systolic dysfunction was not significantly associated with recurrent stroke after adjustment for imbalanced covariates (hazard ratio, 1.3 [95% CI, 0.7–2.4]). Compared with aspirin, apixaban was associated with a significantly reduced risk of recurrent ischemic stroke in patients with LV systolic dysfunction (hazard ratio, 0.24 [95% CI, 0.07–0.87]) but not in those without LV systolic dysfunction (hazard ratio, 1.13 [95% CI, 0.65–1.96]; $P_{interaction}$=0.028).

CONCLUSIONS: In a secondary analysis of the ARCADIA trial data, apixaban was associated with a significantly lower risk of recurrent ischemic stroke than aspirin in patients with LV systolic dysfunction.

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

Key Words: cerebral infarction ■ fibrinolytic agents ■ hemorrhage ■ ischemic stroke ■ stroke volume

Patients with left ventricular (LV) systolic dysfunction are at risk for recurrent stroke through cardiac embolization,[1,2] yet the optimal treatment to prevent embolization and recurrent stroke is uncertain.[3] Secondary analyses of clinical trials such as WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) and COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death,

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Nonstandard Abbreviations and Acronyms

ARCADIA	Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke
COMMANDER HF	A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure
HR	hazard ratio
IQR	interquartile range
LV	left ventricle
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
NT-proBNP	N-terminal pro-B-type natriuretic peptide
P-Y	person-years
WARCEF	Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction
WMA	wall motion abnormality

Myocardial Infarction, or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) suggest that anticoagulation may be beneficial at reducing the risk of ischemic stroke but is associated with a heightened risk of major hemorrhage.[4–7] These trials, however, focused on only one type of LV systolic dysfunction, namely, low ejection fraction, and the majority of enrolled participants had no history of stroke at baseline, resulting in low event rates.[4,5] These trials did not include other, more common forms of LV systolic dysfunction such as segmental wall motion abnormalities (WMAs), for which the optimal secondary stroke preventive therapy is unknown. In an exploratory analysis of the NAVIGATE ESUS trial, rivaroxaban 15 mg versus aspirin was associated with a reduced risk of recurrent stroke in patients with LV systolic dysfunction defined by WMA or global contractility impairment of the LV. However, <100 patients had LV systolic dysfunction, and the rate of major bleeding with rivaroxaban in the trial was significantly higher than with aspirin.[8] Due to limited evidence, guidelines remain equivocal regarding secondary stroke preventive therapy in patients with reduced LV ejection fraction (LVEF), with no recommendations regarding the optimal secondary stroke preventive therapy in patients with other forms of LV systolic dysfunction such as WMA.[3] This uncertainty results in wide variation in clinical practice in the use of secondary stroke preventive antithrombotic therapies in patients with LV systolic dysfunction.[9]

ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) was a secondary stroke prevention trial evaluating the efficacy of apixaban versus aspirin in patients with cryptogenic stroke and markers of atrial cardiopathy.[10] Although the trial showed no difference in the efficacy of apixaban and aspirin, there was also no significant increase in major hemorrhages with apixaban. We used data from the ARCADIA trial to evaluate whether apixaban was associated with a lower risk of recurrent ischemic stroke compared with aspirin in patients with LV systolic dysfunction.

METHODS

Study Design and Population

This is a post hoc exploratory analysis of the ARCADIA trial. ARCADIA was a phase 3, double-blind randomized controlled trial conducted at 185 sites in the National Institutes of Health StrokeNet and the Canadian Stroke Consortium from February 2018 to December 2022.[6] The StrokeNet Central Institutional Review Board, Health Canada, and institutional review boards or research ethics boards at participating sites approved the study protocol. All patients or their surrogates provided informed consent. The ARCADIA clinical trial data set is available through application to the trial's ancillary study committee. The data set for public use will be posted to the NINDS Archived Clinical Research Dataset Repository within 2 years of database lock. This secondary analysis was adherent to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Patients were eligible for randomization in ARCADIA if they were aged ≥45 years, had a cryptogenic ischemic stroke meeting criteria for embolic stroke of undetermined source after standard investigation including echocardiography, and had at least 1 marker of atrial cardiopathy.[8,11] Relevant exclusion criteria were atrial fibrillation and LVEF <30%. Atrial cardiopathy was defined by the presence of one of the following markers: (1) P-wave terminal force on electrocardiogram lead V_1 >5000 μV×ms, (2) serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) >250 pg/mL, or (3) left atrial diameter index ≥3 cm/m^2 by echocardiography.

In this analysis, patients were included if they had documentation of LV systolic function, defined by having an LVEF or LV fractional shortening (LVFS) available in the data set.

Intervention

Patients who met eligibility criteria were randomized in a 1:1 ratio to either standard dose apixaban (5 mg twice daily unless standard dose reduction criteria were met for 2.5 mg twice daily) or aspirin. The dose of aspirin was 81 mg once daily.

Outcomes

The primary efficacy outcome for this secondary analysis was recurrent ischemic stroke. The secondary outcomes included (1) recurrent stroke (hemorrhagic, ischemic, or undetermined) or systemic embolism, (2) symptomatic intracranial hemorrhage

including symptomatic hemorrhagic transformation of an ischemic stroke, and (3) major hemorrhage other than intracranial hemorrhage. Symptomatic intracranial hemorrhage was defined by extravascular blood in the cranium associated with and identified as the predominant cause of a new neurologic symptom, which included headache and death. Major hemorrhage was defined in a standard fashion.[12]

Exposures

The primary exposure was LV systolic dysfunction at baseline, defined as the composite of ≥1 of the following echocardiographic findings: (1) LVEF <50%, (2) reduced LVFS <25%, or (3) LV WMA. Per the trial's protocol, images of the first technically adequate poststroke echocardiogram were sent by sites to ARCADIA's Echocardiography Core, which centrally quantified LVEF and LVFS values.[10] We selected a maximal LVEF threshold of 50% because LVEF below this threshold was previously linked with an increased risk of ischemic stroke.[13] While heart failure with reduced ejection fraction has been defined by an established threshold of LVEF <40%, the 2022 guidelines for heart failure management include therapeutic recommendations for LVEF up to 49%.[14] LVFS is a measurement of LV systolic function using 2-dimensional echocardiography, with fractional shortening defined as ([LV internal diameter at end diastole—LV internal diameter at end systole]/[LV internal diameter at end diastole])×100%.[15] LVEF can be approximately derived by multiplying LVFS by the value of 2; hence, we selected an LVFS <25% cutoff in alignment with the LVEF <50% threshold.[16,17] A dedicated variable to record the presence of WMA was not included in the ARCADIA case report forms. To extract the presence and characteristics of WMA, we searched comments made by the central echocardiography reviewers (Supplemental Methods; Table S1).[18] The secondary exposures of interest were the individual 3 LV systolic dysfunction subtypes (LVEF <50%, LVFS <25%, and any LV WMA).

Covariates

We compared baseline characteristics of patients with and without each LV systolic dysfunction exposure that may be associated with the outcomes of interest. These included age, sex, race, ethnicity, weight, and the comorbidities of hypertension, prior or current tobacco use, diabetes, prior stroke, coronary artery disease, heart failure, and peripheral artery disease. The CHA_2DS_2-VASc score as a composite covariate was also included.[19] Poststroke characteristics were the presenting National Institutes of Health Stroke Scale, markers of left atrial cardiopathy including serum N-terminal-pro-B-natriuretic peptide level, P-wave terminal force in lead V_1, left atrial diameter index, and days from index stroke to randomization.

Statistical Analysis

The baseline characteristics of patients in the analytic intention-to-treat cohort, stratified by LV systolic dysfunction status at baseline, were summarized using means and SDs or medians and interquartile ranges (IQRs) for continuous variables, as appropriate, and counts and proportions for categorical variables. No missing data were imputed. The Student *t* test or the Wilcoxon rank-sum test, as appropriate, was used to compare continuous variables or the Pearson χ^2 test for categorical variables between patients with and without LV systolic dysfunction. Incidence rates of the primary outcome were calculated in each subgroup defined by the presence or absence of LV systolic dysfunction. To describe the spectrum of LV systolic dysfunction present, we characterized the frequencies of all combinations of individual and multiple LV systolic dysfunction subtypes in the subset of patients with nonmissing values for LVEF, LVFS, and WMA. We tested the Spearman rank correlation of the continuous variables of LVEF and LVFS.

We built a Cox proportional hazard model to evaluate the association between the LV systolic dysfunction exposures and recurrent ischemic stroke risk. This model was then adjusted for covariates that were imbalanced between the primary exposure groups in descriptive analysis at a prespecified $P_{threshold}<0.05$.[8] In a sensitivity analysis, we also performed an adjustment of any significant unadjusted model using traditional predictors for recurrent stroke: age, sex, race, ethnicity, prior stroke, and diabetes. We also explored the associations between LV systolic dysfunction exposures and recurrent ischemic stroke risk within randomization strategy subgroups. We tested whether the proportionality hazard assumption was met by including an interaction term between LV systolic dysfunction and time, and no violations were observed. The exposures of LVEF and LVFS were also explored as continuous variables. If significant, restricted cubic splines were fit to delineate the association between each exposure as a continuous variable and the hazard ratios (HRs) of recurrent ischemic stroke at the aforementioned dichotomization thresholds and first and 99th percentile distribution of the exposure in our cohort.

To explore heterogeneity in treatment effect, we built Cox proportional hazard models to determine the association between the randomized treatment strategy and the primary outcome in patients with and without LV systolic dysfunction. We evaluated whether treatment effects were modified by LV systolic dysfunction status by constructing an interaction term of LV systolic dysfunction status×treatment strategy and ascertaining its *P* value. We opted not to adjust for baseline covariates, given that the trial's treatment randomization strategy resulted in balanced covariates in the apixaban and aspirin intention-to-treat groups.[10] We used the same approach to determine the associations between the randomized treatment strategy and the primary outcome within the 3 LV systolic dysfunction subtypes. Sensitivity analyses were performed excluding 4 patients randomized despite a central laboratory measurement of LVEF <30%. Statistical analyses were performed using Stata (StataCorp, 2017, Stata Statistical Software: Release 15.1, College Station, TX) and R (version 4.3.2, 2023, The R Foundation for Statistical Computing). A 2-sided $P<0.05$ was considered statistically significant. Given the exploratory nature of these analyses, no correction was made for multiple comparisons.

RESULTS

A total of 3745 patients consented for ARCADIA (Figure S1). Of the 1015 patients randomized into the treatment phase of ARCADIA, a total of 964 patients met the inclusion criteria for this analysis. Among these patients, 165 (17.1%) had LV systolic dysfunction, and 799 (82.9%) did not (Table S2). The median time (IQR)

from randomization to follow-up was 1.72 (0.66–3.38) years in patients with LV systolic dysfunction and 1.49 (0.67–2.85) years in those without LV systolic dysfunction. While LVEF <30% was an exclusion criterion, upon central review by the trial's echocardiography core, 4 patients with LVEF <30% (minimum 24%) were randomized. A total of 65 recurrent ischemic strokes occurred during follow-up.

Characteristics of Patients Stratified by LV Systolic Dysfunction

Patients with and without LV systolic dysfunction differed significantly by sex and race (Table 1). Patients with LV systolic dysfunction compared with those without were significantly more likely to have a history of coronary artery disease and heart failure and to have higher values for NT-proBNP and left atrial diameter index. Median LVEF in patients with LV systolic dysfunction was 52% (IQR, 45%–60%) and 62% (IQR, 59%–65%) among those without LV systolic dysfunction.

The most common abnormality was LVFS either alone or in combination with other subtypes. The Spearman rank correlation between LVEF and LVFS was 0.37 (P<0.001), indicating a moderate correlation between these 2 measures (Figure S2). Among patients with WMA (n=57), the most frequent severity grade was hypokinesis (65%), and the most frequent region involved was the apex (38.6%; Table S3).

Table 1. Baseline Characteristics of Patients With and Without LV Systolic Dysfunction

Baseline characteristics	No LV systolic dysfunction (N=799)	LV systolic dysfunction (N=165)	*P* value
Age, y; mean (SD)	68 (11)	67 (11)	0.206
Female	450 (56.3)	71 (43.0)	0.002
Race			0.011
Black	159 (19.9)	46 (27.9)	
White	610 (76.4)	108 (65.5)	
Other	30 (3.8)	11 (6.7)	
Ethnicity			0.404
Non-Hispanic	730 (91.4)	154 (93.3)	
Hispanic	69 (8.6)	11 (6.7)	
Weight, kg	83 (70–97)	84 (72–100)	0.250
Hypertension	608 (76.1)	137 (83.0)	0.053
Prior or current tobacco use	331 (41.4)	77 (46.7)	0.215
Diabetes	240 (30.0)	58 (35.2)	0.196
Prior stroke or TIA	150 (18.8)	32 (19.4)	0.853
Coronary artery disease	56 (7.0)	42 (25.5)	<0.001
Heart failure	31 (3.9)	36 (21.8)	<0.001
Peripheral artery disease	13 (1.6)	3 (1.8)	0.861
CHADSVasc, median (IQR)	5 (4–6)	5 (4–6)	0.083
NIHSS score, median (IQR)	1 (0–3)	1 (0–2)	0.195
NT-proBNP, pg/mL; median (IQR)	286 (90–520)	419 (262–928)	<0.001
PTFV1, μV×ms; median (IQR)	5225 (2925–6000)	4125 (2200–6000)	0.060
Left atrial diameter index, cm/m^2; median (IQR)	1.9 (1.7–2.1)	2.0 (1.8–2.2)	0.002
Days from index stroke to randomization, median (IQR)	50 (22–99)	46 (19–90)	0.253

IQR indicates interquartile range; LV, left ventricle; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and PTFV1, p-wave terminal force in V_1.

Outcomes Among Patients With and Without LV Systolic Dysfunction

Frequencies and incidence rates for the primary outcomes by the composite and the 3 individual LV systolic dysfunction subtypes are presented in Table 2 and Table S4. Among patients with LV systolic dysfunction (n=165), 15 (9.1%) experienced the primary outcome (incidence rate of 4.6 per 100 person-years [P-Y]). Among patients without LV systolic dysfunction (n=799), 50 (6.3%) patients experienced the primary outcome (incidence rate of 3.6 per 100 P-Y). Frequencies and incidence rates associated with the individual LV systolic dysfunction subtypes are presented in Table 2 and Table S4.

Cumulative rates of recurrent ischemic stroke as functions of LV systolic dysfunction and each of the 3 subtypes are depicted in Kaplan-Meier curves in Figure 1. Only reduced LVEF was associated with a significantly elevated risk of recurrent ischemic stroke (adjusted HR, 2.6 [95% CI, 1.2–5.6]; Table 2). In the sensitivity analysis, reduced LVEF adjusted for traditional risk factors remained statistically significant (adjusted HR, 2.07 [95% CI, 1.04–4.15]; P=0.038). In addition, only LVEF as a continuous variable was significantly associated with the hazard of recurrent ischemic stroke (unadjusted HR, 0.97 [95% CI, 0.94–0.99]). A restricted cubic spline demonstrates an average HR of 1.18 between LVEF 32% and 50% and an average HR of 0.65 between LVEF 50% and 74% (Figure S3). The HR was consistently >1 when LVEF was <50% and <1 when LVEF was >50%.

We explored the associations between LV systolic dysfunction and the risk of recurrent ischemic stroke within randomization strategy subgroups (Table S5). In the aspirin subgroup, the composite LV systolic dysfunction, reduced LVEF, and reduced LVFS were significantly associated with at least a 2-fold increased risk of recurrent ischemic stroke in unadjusted analyses; however, upon adjusting for imbalanced covariates, only the association between reduced LVEF and recurrent ischemic stroke risk remained significant (HR, 2.8 [95% CI, 1.2–5.6]). There was no heightened risk of recurrent ischemic stroke observed with any of the LV systolic dysfunction types in the apixaban subgroup.

Table 2. Risk of Recurrent Ischemic Stroke as a Function of LV Systolic Dysfunction Subtypes

LV systolic dysfunction composite and subtypes	Incident outcomes among exposed, %	Incident outcomes among unexposed, %	Unadjusted HR (95% CI)*	Adjusted HR (95% CI)*
Composite LV systolic dysfunction	15/165 (9.1)	50/799 (6.3)	1.4 (0.8–2.4)	1.3 (0.7–2.4)
LVEF <50%	10/73 (13.7)	55/889 (6.2)	2.2 (1.1–4.3)	2.6 (1.2–5.6)
LVFS <25%	10/128 (7.8)	53/816 (6.5)	1.2 (0.6–2.3)	1.1 (0.6–2.3)
LV WMA	6/57 (10.5)	59/907 (6.5)	1.4 (0.6–3.2)	1.2 (0.5–3.1)

HR indicates hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and WMA, wall motion abnormality.

*HR and 95% CI from Cox proportional hazard models without and with limited adjustment for imbalanced covariates given the small number of outcomes: (1) composite LV systolic dysfunction model adjusted for sex, race, coronary artery disease, congestive heart failure, NT-proBNP, and left atrial diameter index; (2) LVEF model adjusted for age, sex, race, coronary artery disease, congestive heart failure, NT-proBNP, and left atrial diameter index; (3) LVFS model adjusted for age, sex, coronary artery disease, congestive heart failure, National Institutes of Health Stroke Scale at presentation, NT-proBNP, P-wave terminal force in V_1, and left atrial diameter; and (4) WMA model adjusted for age, sex, race, coronary artery disease, congestive heart failure, NT-proBNP, and left atrial diameter index.

Treatment Effect Stratified by the Presence or Absence of LV Systolic Dysfunction

The baseline characteristics of patients with and without LV systolic dysfunction stratified by randomized treatment strategy were similar, except that among patients with LV systolic dysfunction, those randomized to apixaban were significantly more likely to be Hispanic (10.8% versus 2.4%; *P*=0.03; Table S6), and among patients without LV dysfunction, those randomized to apixaban had a slightly larger left atrial diameter index (among those without LV systolic dysfunction, apixaban versus aspirin: median, 1.92 [IQR, 1.70–2.13] versus median, 1.85 [IQR 1.66–2.07]; *P*=0.011).

Among patients with LV systolic dysfunction on aspirin (N=82), 12 (14.6%) had a primary outcome (incidence rate of 7.6 per 100 P-Y; Table S4). For those with LV systolic dysfunction on apixaban (N=83), 3 (3.6%) had a primary outcome (incidence rate of 1.8 per 100 P-Y). For patients without LV systolic dysfunction on aspirin (N=407), 24 (5.9%) had a primary outcome (incidence rate of 3.4 per 100 P-Y). For patients without LV systolic dysfunction on apixaban (N=392), 26 (6.6%) had a primary outcome (incidence rate of 3.8 per 100 P-Y).

In patients with LV systolic dysfunction, the risk of recurrent ischemic stroke among patients randomized to apixaban versus aspirin was significantly reduced (HR, 0.24 [95% CI, 0.07–0.87]; Table 3). In patients without LV systolic dysfunction, the risk of recurrent ischemic stroke among patients randomized to apixaban versus aspirin was not significantly different (HR, 1.13 [95% CI, 0.65–1.96]). The *P* value for the interaction term was 0.028, indicating that LV systolic dysfunction status significantly modified the effect of apixaban versus aspirin. The Kaplan-Meier curves stratified by LV systolic dysfunction status are presented in Figure 2.

We examined the associations of treatment strategy and the primary outcome in the 3 LV systolic dysfunction subtypes (Table 3; Figure 2). In patients with LVFS <25%, the risk of recurrent ischemic stroke was significantly lower among patients randomized to apixaban compared with aspirin (HR, 0.11 [95% CI, 0.01–0.83]), while the risk was similar for those with LVFS ≥25% (HR, 1.09 [95% CI, 0.64–1.87]; $P_{interaction}$=0.029). There were nonsignificant trends toward reduced risk of the primary outcome with apixaban compared with aspirin with LVEF <50% (HR, 0.45 [95% CI, 0.12–1.76]) and LV WMA (HR, 0.22 [95% CI, 0.03–1.88]).

In terms of secondary outcomes, the rates of recurrent stroke of any type were similar to those of recurrent ischemic stroke (Table S7). Among patients with LV systolic dysfunction, the percentages of patients with sICH were 1.2% (n=1) for both those randomized to apixaban and aspirin. Among those without LV systolic dysfunction, comparable percentages were 0.5% (n=2) with apixaban and 0.7% (n=3) with aspirin. Among those with LV systolic dysfunction, the percentages of patients with major hemorrhages were 1.2% (n=1) with apixaban and 2.4% (n=2) with aspirin. Among those without LV systolic dysfunction, comparable percentages were 1.0% (n=4) with apixaban and 0.7% (n=3) with aspirin.

In sensitivity analyses of the cohort excluding the 4 patients with LVEF <30%, the results for stroke risk and treatment associations remained unchanged (Table S8).

DISCUSSION

In this secondary analysis of patients with cryptogenic stroke and evidence of atrial cardiopathy who were randomized in the ARCADIA trial, apixaban was associated with a lower risk of recurrent stroke than aspirin in patients with LV systolic dysfunction and LVEF ≥30%, whereas the risk of recurrent stroke was similar in patients randomized to apixaban versus aspirin in patients without LV systolic dysfunction.

ORIGINAL CONTRIBUTION

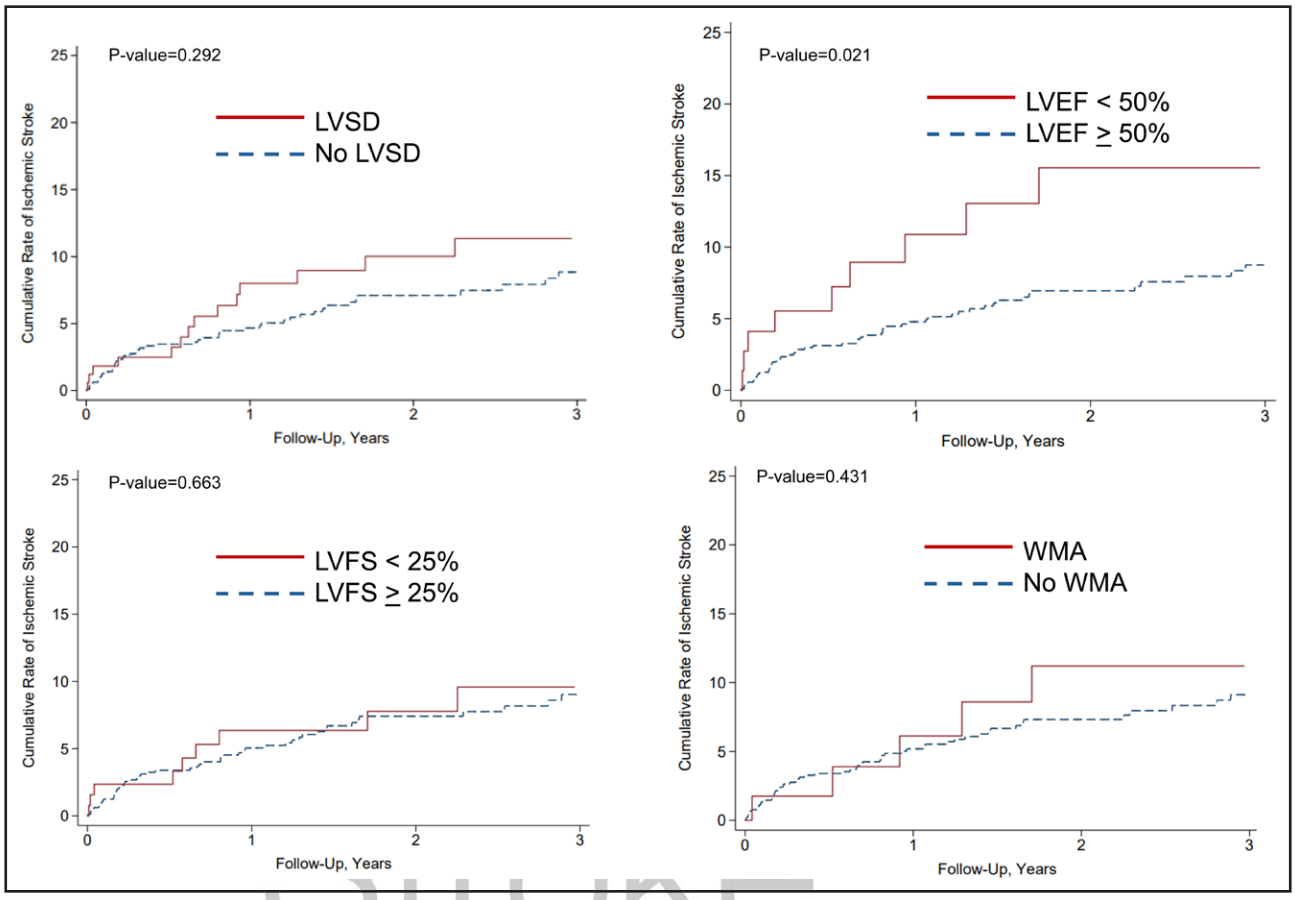

Figure 1. XXX.
Kaplan-Meier curves of recurrent ischemic stroke risk stratified by left ventricular (LV) systolic dysfunction (LVSD) status (top left), LV fractional shortening (LVFS; <25% vs ≥25%; bottom left), LV ejection fraction (LVEF; <50% vs ≥50%; top right), and wall motion abnormality (WMA; bottom right).

Our study adds to the literature, indicating that anticoagulation may be superior to antiplatelet therapy for reducing recurrent stroke risk in patients with LV systolic dysfunction. While primary prevention trials such as WARCEF and COMMANDER HF showed no overall benefit of anticoagulation over antiplatelet

Table 3. Hazard Ratios of Recurrent Ischemic Stroke Stratified by LV Systolic Dysfunction Subtype as a Function of Treatment Strategy and *P* Values of Their Interactions

LV systolic dysfunction composite and subtypes	Incident outcomes in apixaban arm (frequency)	Incident outcomes in aspirin arm (frequency)	Hazard ratio (95% CI)	$P_{interaction}$ value
Composite LV systolic dysfunction				0.028
Present (n=165)	3 (3.6)	12 (14.6)	0.24 (0.07–0.87)	
Absent (n=799)	26 (6.6)	24 (5.9)	1.13 (0.65–1.96)	
LV ejection fraction				0.333
<50% (n=73)	3 (8.6)	7 (18.4)	0.45 (0.12–1.76)	
≥50% (n=889)	26 (5.91)	29 (6.5)	0.91 (0.54–1.55)	
LV fractional shortening				0.029
<25% (n=128)	1 (1.6)	9 (13.9)	0.11 (0.01–0.83)	
≥25% (n=816)	27 (6.8)	26 (6.3)	1.09 (0.64–1.87)	
LV wall motion abnormality				0.192
Present (n=57)	1 (3.7)	5 (16.7)	0.22 (0.03–1.88)	
Absent (n=865)	28 (6.3)	31 (6.8)	0.92 (0.55–1.53)	

LV indicates left ventricle.

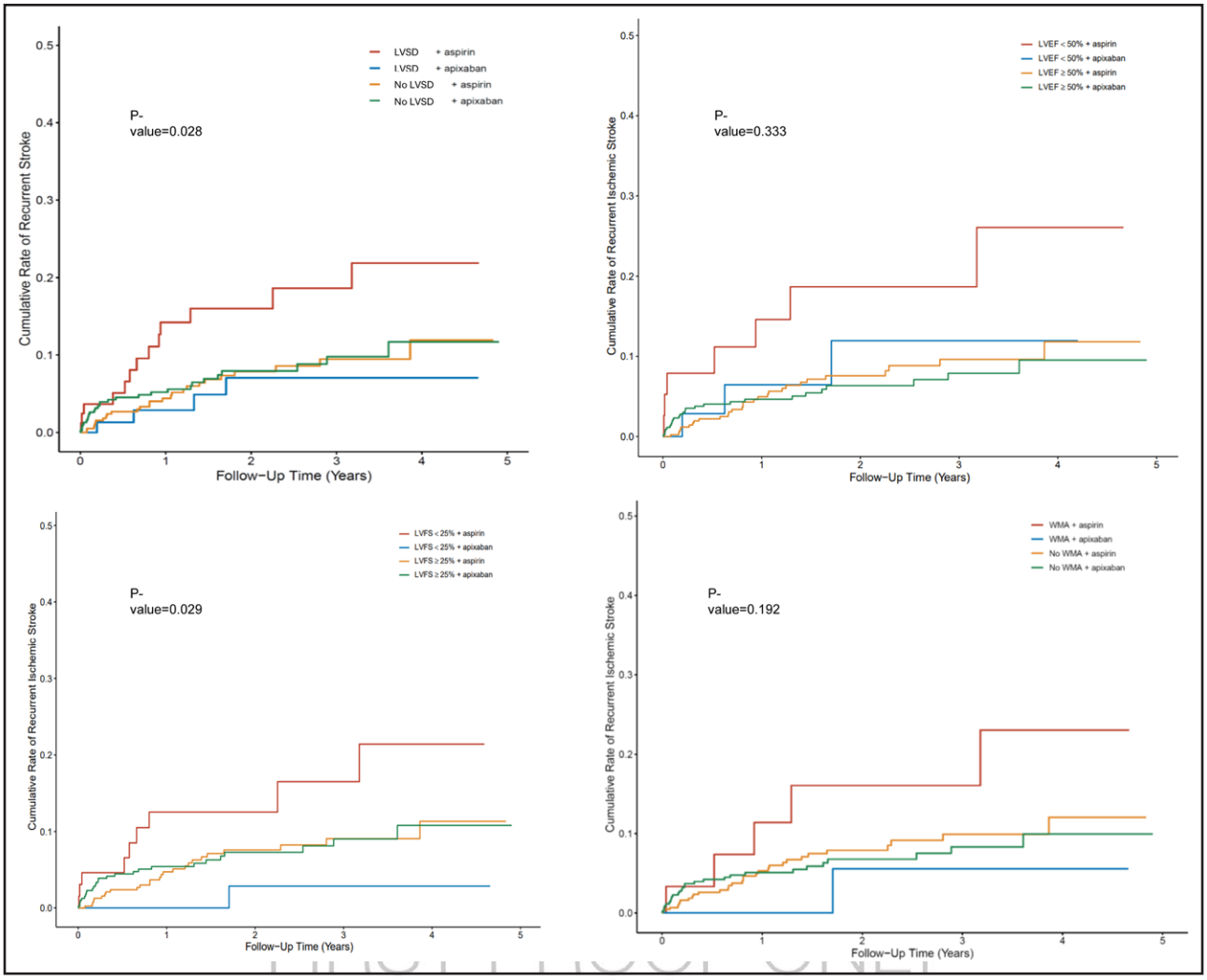

Figure 2. XXX.
Kaplan-Meier curves of treatment effect stratified by left ventricular (LV) systolic dysfunction (LVSD) status (top left), LV fractional shortening (LVFS; <25% vs ≥25%; bottom left), LV ejection fraction (LVEF; <50% vs ≥50%; top right), and wall motion abnormality (WMA; bottom right).

therapy in patients with reduced LVEF, secondary analyses of these trials suggested that anticoagulation may be superior at reducing ischemic stroke risk, albeit with a heightened risk of major hemorrhage.[7] As a result, guidelines continue to be equivocal regarding the optimal secondary stroke preventive therapy in patients with reduced ejection fraction. In an exploratory analysis of NAVIGATE ESUS, rivaroxaban was superior to antiplatelet therapy at reducing the risk of recurrent stroke (HR, 0.36 [95% CI, 0.14–0.93]) in patients with LV systolic dysfunction, but only a fraction of patients enrolled in the trial had LV systolic dysfunction (7.1%), and LVEF values were not available.[8] Our study is novel for using a broader definition of LV systolic dysfunction compared with prior studies.[20] While prior trials have focused exclusively on reduced LVEF as a source for cardiac embolism and subsequent stroke, various other forms of LV systolic dysfunction are common and have been shown to be associated with a heightened risk of recurrent stroke.[2,8,21] Our results from this ARCADIA analysis provide new data, indicating that apixaban may be superior to aspirin in preventing recurrent ischemic stroke among those with LV systolic dysfunction. Importantly, the bleeding rate was similar with apixaban compared with aspirin, unlike in previous studies. Nevertheless, these results may indicate a net clinical benefit of a direct oral anticoagulant such as apixaban for stroke prevention with LV systolic dysfunction, but a dedicated clinical trial is necessary to confirm this hypothesis.

Our study was novel in its use of a broad definition of LV systolic dysfunction. Various types of LV systolic dysfunction other than reduced LVEF are common, are associated with an elevated risk of stroke via cardiac embolism, and may be targetable using anticoagulation.[2,8,21] In the NAVIGATE ESUS substudy, the inclusion criteria were LV global contractility impairment and WMA. The majority of patients (81%) with LV systolic

dysfunction were included due to WMA alone. Although the heterogeneity in treatment effect within LV systolic dysfunction subgroups results from this ARCADIA analysis was driven by patients with reduced LVFS, a trend was evident toward lower risk of recurrent ischemic stroke in the LVEF < 50% and WMA randomized to apixaban, albeit without statistical significance likely due to being underpowered. The risk of recurrent ischemic stroke was heightened among those patients with any LV systolic dysfunction, reduced LVEF, and reduced LVFS by >2-fold in unadjusted analysis, while there was no significant increased risk of recurrent ischemic stroke among patients in the apixaban subgroup with LV systolic dysfunction. There was also a nonsignificant trend of increased risk among those randomized to aspirin even with WMA (HR, 2.2 [95% CI, 0.8–5.6]). Upon adjustment, the risk of reduced LVEF in the aspirin group remained significant. These exploratory findings may be a signal that aspirin may not be sufficient for ischemic stroke prevention among those with LV systolic dysfunction. LV systolic dysfunction represented by a variety of echocardiographic measures may indicate a spectrum associated with graded stroke pathogenicity. The wall motion score index is a scoring system based on myocardial thickening.[22] Studies demonstrate that a higher wall motion score index is directly associated with the likelihood of LV thrombus formation.[23,24] The paucity of events per combination of LV systolic dysfunction subtypes precluded an analysis of the gradation of stroke risk by the burden of subtypes. While the heterogeneity of treatment effect was driven by the low LVFS subtype, further studies are needed to validate this previously undescribed finding.

This study has limitations. It was a post hoc, exploratory analysis of subgroups from a randomized controlled trial data set; thus, our findings are hypothesis-generating and do not imply causality. The number of patients with LV systolic dysfunction was relatively small and even more so for each of the 3 individual LV systolic dysfunction subtypes. Ascertainment of LV systolic dysfunction by echocardiography may be subject to inter-rater variability.[25] Possibly, the low bleeding risk with apixaban in select patients with cryptogenic stroke, left atrial cardiopathy, and LV dysfunction that is not severe may not generalize to a higher risk population of patients with LVEF <30%, who may harbor a higher bleeding risk in the setting of end-organ injury to the brain, kidney, and liver.[26] We did not account for the degree of medication adherence. No repeat echocardiography was available to determine whether the LV systolic dysfunction noted on echocardiography at the time of the index ischemic stroke evaluation was transient. Last, LVFS is a surrogate marker of LV function that requires the ventricular geometry to be normal and no WMAs to accurately reflect LV function, and some of these data were missing from the study.

CONCLUSIONS

In this secondary analysis of the ARCADIA trial of patients with recent cryptogenic stroke and atrial cardiopathy, the risk of recurrent ischemic stroke was reduced with apixaban compared with aspirin in patients with LV systolic dysfunction.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
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