

Coagulation markers and echocardiography predict atrial fibrillation, malignancy or recurrent stroke after cryptogenic stroke

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Abstract

We evaluated the utility of left atrial volume index (LAVI) and markers of coagulation and hemostatic activation (MOCHA) in cryptogenic stroke (CS) patients to identify those more likely to have subsequent diagnosis of atrial fibrillation (AF), malignancy or recurrent stroke during follow-up.

Consecutive CS patients who met embolic stroke of undetermined source (ESUS) who underwent transthoracic echocardiography and outpatient cardiac monitoring following stroke were identified from the Emory cardiac registry. In a subset of consecutive patients, d-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex and fibrin monomer (MOCHA panel) were obtained ≥ 2 weeks post-stroke and repeated ≥ 4 weeks later if abnormal; abnormal MOCHA panel was defined as ≥ 2 elevated markers which did not normalize when repeated. We assessed the predictive abilities of LAVI and the MOCHA panel to identify patients with subsequent diagnosis of AF, malignancy, recurrent stroke or the composite outcome during follow-up.

Of 94 CS patients (mean age 64 ± 15 years, 54% female, 63% non-white, mean follow-up 1.4 ± 0.8 years) who underwent prolonged cardiac monitoring, 15 (16%) had new AF. Severe LA enlargement (vs normal) was associated with AF ($P < .06$). In 42 CS patients with MOCHA panel testing (mean follow-up 1.1 ± 0.6 years), 14 (33%) had the composite outcome and all had abnormal MOCHA. ROC analysis showed LAVI and abnormal MOCHA together outperformed either test alone with good predictive ability for the composite outcome (AUC 0.84).

We report the novel use of the MOCHA panel in CS patients to identify a subgroup of patients more likely to have occult AF, occult malignancy or recurrent stroke during follow-up. A normal MOCHA panel identified a subgroup of CS patients at low risk for recurrent stroke on antiplatelet therapy. Further study is warranted to evaluate whether the combination of an elevated LAVI and abnormal MOCHA panel identifies a subgroup of CS patients who may benefit from early anticoagulation for secondary stroke prevention.

Abbreviations: AF = atrial fibrillation, AUC = area under the curve, CS = cryptogenic stroke, ESUS = embolic stroke of undetermined source, ILR = implantable loop recorder, LAVI = left atrial volume index, MCOT = mobile cardiac outpatient telemetry, MOCHA = markers of coagulation and hemostatic activation, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, TTE = transthoracic echocardiogram, USPSTF = US Preventive Services Task Force.

Keywords: atrial fibrillation, coagulation, cryptogenic stroke, embolic stroke of undetermined significance (ESUS)

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Fadi Nahab contributed to study design, data collection and manuscript preparation.

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Fadi Nahab MD has a patent pending on the use of markers of coagulation and hemostatic activation to guide medical treatment including anticoagulation.

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1. Introduction

Of the 87% of strokes that are ischemic in origin, 30% to 40% are classified as cryptogenic in origin.^[1] In the absence of a clear cause current American Heart Association/American Stroke Association guidelines recommend the combination of antiplatelet therapy and risk factor modification given that prior studies have shown no benefit to anticoagulation.^[2] However, recent studies suggest that cryptogenic stroke (CS) patients may have thromboembolic causes including occult atrial fibrillation (AF), occult malignancies and an estimated recurrent stroke rate of 4% per year despite antiplatelet therapy.^[1,3]

Left atrial structural abnormalities including enlarged left atrial size have been associated with patients more likely to have occult AF however they are limited in identifying other causes of CS.^[4,5] Markers of coagulation and hemostatic activation (MOCHA) tests have previously been shown to increase in patients with AF, cancer or cardioembolic stroke however there is limited data on their use in CS patients.^[6–10] The objective of our study was to evaluate left atrial size and MOCHA tests in their ability to identify a subgroup of CS patients who are more likely to have subsequent detection of occult AF, occult malignancy or recurrent stroke.

2. Methods

2.1. Participants

Consecutive CS patients according to embolic stroke of undetermined source (ESUS) criteria^[11] seen in the Emory Clinic from January 1, 2015 to December 31, 2016 were included in this analysis if they were ≥ 18 years of age and completed prolonged outpatient cardiac monitoring with either 30-day mobile cardiac outpatient telemetry (MCOT) and/or implantable loop recorder (ILR) (Reveal LINQ, Medtronic, Minneapolis, MN) from the Emory cardiac registry. Briefly, all patients underwent brain imaging with a CT or MRI that displayed a non-lacunar brain infarct that excluded extra- and intracranial arterial stenosis or occlusion due to atherosclerosis, vasculitis, dissection, and excluded a documented cardioembolic source after 12-lead ECG, cardiac monitoring for ≥ 24 h with automated rhythm detection and echocardiography. Beginning January 1, 2016 we

initiated the MOCHA panel as part of our CS workup measuring serum levels of d-dimer (reference value < 500 ng/mL), prothrombin fragment 1.2 (reference value 65–288 pmol/L), thrombin-antithrombin complex (reference value 1.0–5.5 mcg/L) and fibrin monomer (reference value < 7 mcg/mL) ≥ 2 weeks after stroke onset. If any of the initial 4 markers were elevated, the panel was repeated ≥ 4 weeks after initial testing to determine whether there was persistent elevation in markers or normalization. For this analysis we excluded patients on anticoagulation therapy at the time of MOCHA testing and patients with history of venous thromboembolism.

2.2. Echocardiography

Standard 2-dimensional and Doppler transthoracic echocardiography (TTE) was performed on a GE Vivid 7 and E9 (General Electric, Milwaukee, WI) or Philips IE 33 (Philips, Andover, MA). We evaluated LA echocardiographic parameters obtained by TTE including left atrial volume index (LAVI) and left atrial diameter. A bubble study was performed to evaluate the presence of a patent foramen ovale and was considered positive if seen on TTE or transesophageal echocardiography. All echocardiography imaging was reviewed by a board-certified cardiologist.

2.3. Measurement of plasma concentrations of MOCHA markers

All assays were done using 3.2% citrated plasma. Plasma D-dimer levels were measured using high sensitivity latex dimer assay (Instrumentation Laboratories, Bedford, Massachusetts). Prothrombin fragment 1.2 and thrombin antithrombin complexes were both performed using the Enzygnost ELISA kit (Siemens Healthcare, Tarrytown, New York, NY). Soluble fibrin monomer was performed using the latex immunoassay (Stago, Parsippany, NJ).

2.4. Patient monitoring and follow-up

Outpatient follow-up after hospitalization was performed according to our CS algorithm (Fig. 1). At outpatient clinic visits, CS patients were encouraged to remain updated on age

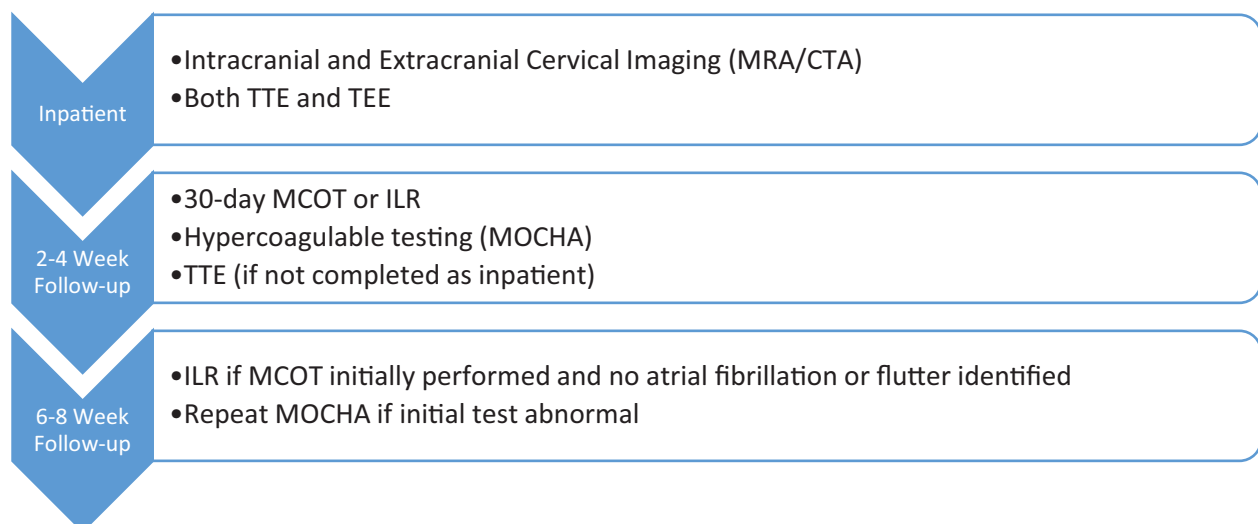


Figure 1. Emory clinic recommended diagnostic testing for cryptogenic stroke.

appropriate cancer screenings as suggested by the US Preventive Services Task Force (USPSTF),^{12]} cardiac monitoring reports were reviewed for evidence of new AF, and history and neurological examination was obtained to identify potential signs of new stroke. All diagnoses were verified by specialists including a board-certified cardiac electrophysiologist for AF, board-certified oncologist for malignancy and board-certified neurologist for stroke.

2.5. Standard protocol approvals, registrations, and patient consents

This study was approved by the Emory Institutional Review Board.

2.6. Statistical analysis

This is a retrospective analysis of prospectively collected data. Comparisons of baseline characteristics and vascular risk factors of our cohort were compared between those who underwent MOCHA panel testing and those who did not. All continuous variables were assessed for normality of distribution; specifically, if the Shapiro-Wilk test P -value was $<.05$, medians and IQR were reported and non-parametric statistical tests were performed. For pairwise non-parametric comparison, the Mann-Whitney U test was performed. For >2 group comparisons, the Kruskal-Wallis test was performed with post-hoc pairwise comparisons using Bonferroni correction. Two-sample t tests were used for continuous variables and Chi-square (or Fisher exact test) was used for categorical variables. A univariable analysis was performed to identify baseline characteristics and echocardiographic parameters associated with newly diagnosed AF during follow-up. Within the CS subgroup of patients who had MOCHA testing, we assessed the number of elevated MOCHA markers in each patient based on initial testing and then based on repeat testing. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were quantified at 0, 1, 2, 3, and 4 elevated markers and obtained for both the initial MOCHA test and based on repeat testing. The usefulness of echocardiographic and MOCHA markers was tested by using receiver operating characteristic (ROC) analysis. In patients with MOCHA tested, we employed forward stepwise logistic regression (Likelihood Ratio method, entry threshold $P < .2$ and $P < .15$

for retention in the model) to identify independent predictors of each outcome including these univariate predictors as well as other potential risk factors such as diabetes, hypertension, hyperlipidemia, PFO and migraine. P values were calculated and statistical significance was determined using $P < .05$.

3. Results

During the study period, 94 patients met our study criteria. The mean age was 64 ± 15 years, 54% were female and 63% were non-white (Table 1). At baseline 77% of patients had a history of hypertension, 37% with diabetes, 61% with hyperlipidemia and 34% had either former or active tobacco use. A previous history of ischemic stroke was present in 19% and 18% had a history of coronary artery disease. In our cohort, 65% completed a 30-day MCOT and 62% underwent ILR monitoring, including 38% who underwent ILR placement after completing MCOT if it showed no significant arrhythmia. Echocardiographic parameters showed normal left atrial size in 71% of patients, 16% mild, 10% moderate and 3% with severe LA dilatation. Median LAVI was 24.9, median left ventricle ejection fraction was 60%, median left ventricle end diastolic dimension was 43 mm and bubble study was positive in 21% of patients.

Over a mean follow-up of 1.4 ± 0.8 years, 15 (16%) had newly diagnosed AF detected on outpatient cardiac monitoring, 5 (5.3%) with newly diagnosed malignancy (including 2 breast cancers, liver cancer, AML, metastatic neuroendocrine tumor) and 10 (11%) with a recurrent ischemic stroke (Table 2). Overall, 28 (31%) had the composite outcome of AF, malignancy or recurrent stroke. In univariable analysis, baseline factors associated with subsequent diagnosis of AF included older age ($P < .04$), history of hypertension ($P < .08$), history of migraine ($P < .06$) and severe (vs none) LA dilatation ($P < .06$).

Baseline characteristics of ESUS patients who underwent MOCHA testing ($n = 42$) were similar to patients who did not undergo MOCHA testing earlier in our study except that those tested were younger (60 vs 67 years, $P = .04$), less likely to have coronary artery disease (7 vs 27% , $P = .01$) and previous ischemic stroke (10 vs 27% , $P < .01$) and shorter duration of follow-up [median 400 (IQR 151–553) vs 538 (IQR 397–730) days, non-parametric test $P < .001$](Table 1).

Table 1
Baseline characteristics and follow-up of the study population.

Characteristics	Total N=94	MOCHA tested N=42	No MOCHA tested N=52	P-value
Demographics				
Age, mean (SD)	64 (15)	60 (17)	67 (14)	.04
Female, n (%)	51 (54%)	26 (62%)	25 (48%)	.25
Race, n (%)				
Non-white	59 (63%)	60 (56%)	35 (67%)	.40
BMI, mean (SD)	29.2 (6.2)	28.8 (7.6)	29.6 (5.7)	.55
Comorbidities, n (%)				
Hypertension	72 (77%)	30 (71%)	42 (81%)	.33
Diabetes	35 (37%)	18 (43%)	17 (33%)	.29
Hyperlipidemia	57 (61%)	25 (60%)	32 (62%)	.84
Coronary artery disease	17 (18%)	3 (7.1%)	14 (27%)	.01
Prior ischemic stroke	18 (19%)	4 (9.5%)	14 (27%)	.01
Tobacco (former/active)	32 (34%)	11 (26%)	21 (40%)	.25
ILR	58 (62%)	28 (67%)	21 (58%)	.22
Follow-up duration, median days (IQR)	464 (358-682)	400 (151-553)	538 (397-730)	.001

BMI=body mass index; ILR=implantable loop recorder, MOCHA = markers of coagulation and hemostatic activation.

Table 2
Endpoints stratified by MOCHA markers.

	Total (n = 42)	MOCHA+ (n = 23)*	MOCHA- (n = 19)	P-value
AF	6 (14%)	6 (26%)	0 (0%)	.02
Malignancy	4 (10%)	4 (17%)	0 (0%)	.11
Stroke	6 (14%)	6 (26%)	0 (0%)	.02
AF, malignancy or stroke	14 (33%)	14 (61%)	0 (0%)	.0001

AF = Atrial fibrillation, MOCHA=Markers of coagulation and hemostatic activation.
 *MOCHA+ defined as ≥2 abnormal markers which did not normalize when repeated.

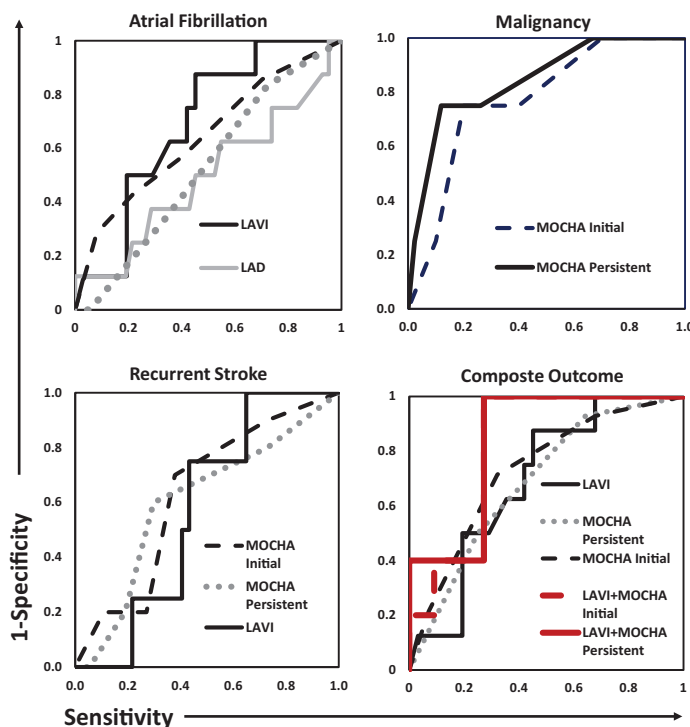
Of patients who underwent MOCHA testing, 23 (55%) had ≥2 elevated markers which did not normalize when repeated; patients with abnormal MOCHA had significantly higher frequency of AF (26 vs 0%, $P < .02$), recurrent stroke (26 vs 0% $P < .02$) and a trend toward higher rates of malignancy (17 vs 0%, $P < .11$) (Table 2). Overall, patients with ≥2 elevated MOCHA markers had significantly higher rates of the composite outcome than patients with less than 2 abnormal markers (61 vs 0%, $P < .0001$). No patients with normal MOCHA panel had any subsequent diagnosis of AF, malignancy, or recurrent stroke during follow-up [NPV 100%].

ROC analysis showed that abnormal MOCHA markers (AUC=0.72) and elevated LAVI (AUC=0.69) had higher discriminative power for the detection of AF than left atrial diameter (AUC=0.50) (Fig. 3). For the detection of malignancy, MOCHA abnormalities also had moderate discriminative power on initial (AUC 0.76) as well as repeat (AUC 0.83) testing showing persistent elevation. For the detection of stroke, MOCHA abnormalities were associated with an AUC 0.63 based on initial testing and AUC 0.64 when repeat MOCHA

testing showed persistent elevation. Together, the combination of elevated LAVI and a persistently abnormal MOCHA panel was associated with a higher AUC for the composite outcome (0.84) compared with any testing alone.

We measured levels of each marker comparing patients with AF or malignancy to those with none of the composite outcome (Fig. 2). Fibrin monomer levels were significantly higher in patients with malignancy ($P < .02$) and AF ($P < .05$) compared with patients who did not have the composite outcome. Thrombin-antithrombin levels had a trend toward higher levels in patients with malignancy compared with no composite outcome ($P < .10$). Levels of d-dimer were significantly higher in AF patients compared to those with none of the composite outcome ($P < .04$) and a trend toward higher levels in malignancy patients ($P < .11$). Prothrombin fragment 1.2 levels had a trend toward increased levels in patients with AF compared to patients with no composite outcome ($P < .08$) but no significant difference in patients with malignancy.

In patients with MOCHA tested, we also employed stepwise regression to identify independent predictors of each outcome. Univariate predictors ($P < .2$) of the composite outcome included MOCHA abnormalities (continuous variable, $P < .04$), age ($P < .12$) and left atrial size ($P < .16$). Using forward stepwise logistic regression including these univariate predictors as well as other potential risk factors including diabetes, hypertension, hyperlipidemia, PFO, and migraine we observed that the final model only retained an abnormal MOCHA profile as a significant predictor of the composite outcome (OR=1.74, 95% CI 1.004–3.015, $P < .048$). For AF as the outcome measure, only severe LA dilatation was identified as a significant predictor (OR=3.51, 95% CI 1.17–10.5, $P < .025$) while MOCHA was not. For new diagnosis of malignancy, MOCHA abnormalities trended towards significance as an independent predictor (OR=



	Atrial Fibrillation	Malignancy	Recurrent Stroke	Composite Outcome*
LAVI	0.69	-	0.62	0.69
LA diameter (cm)	0.50	-	0.52	0.62
MOCHA (initial)	0.72	0.63	0.63	0.72
MOCHA (persistent)	0.53	0.83	0.64	0.71
LAVI + Abnormal MOCHA (initial)	-	-	0.79	0.81
LAVI + Abnormal MOCHA (persistent)	-	-	0.8	0.84

*Composite outcome= Atrial fibrillation, malignancy or recurrent stroke.
 AUC=Area under the curve; LAVI= left atrial volume index; LA=left atrium;
 MOCHA=markers of coagulation and hemostatic activation

Figure 2. Markers of coagulation and hemostatic activation (MOCHA) levels across the outcome measures.

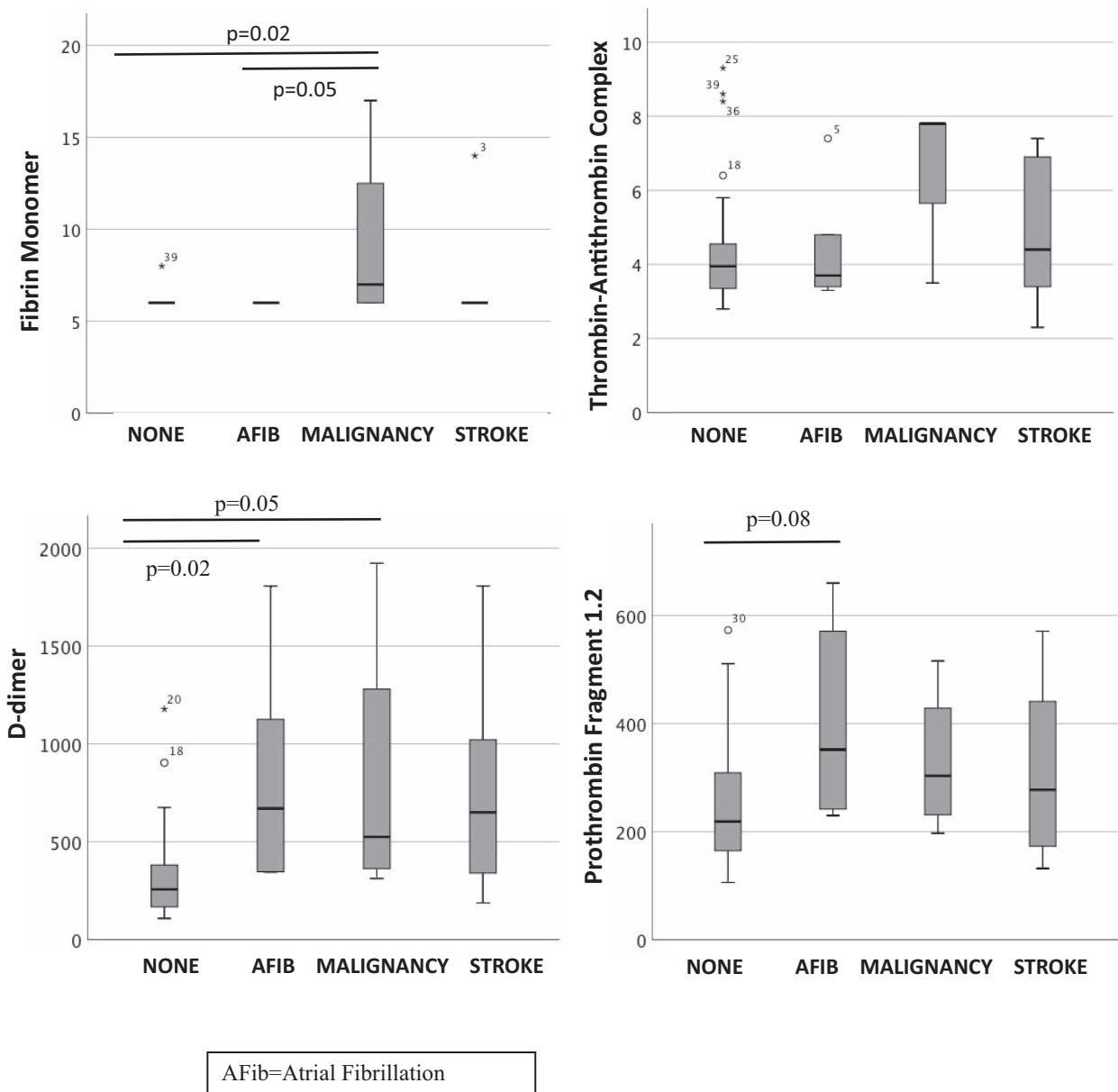


Figure 3. Receiver operator curve analysis of left atrial structural measures, MOCHA levels and endpoints. MOCHA = markers of coagulation and hemostatic activation.

1.99, 95% CI 0.84–4.75, $P < .12$). For recurrent stroke as the outcome, migraine trended towards significance (OR = 5.4, 95% CI 0.84–34, $P < .076$).

4. Discussion

We found that CS patients had a high rate of occult AF, occult malignancy or recurrent stroke with 31% of patients having the composite outcome during follow-up while on antiplatelet therapy. MOCHA marker elevation combined with elevated LAVI seen on echocardiogram had good predictive ability for identifying patients with the composite outcome. Notably, patients with normal MOCHA levels post-stroke had no subsequent endpoints during follow-up with an NPV 100%.

Our study has several important implications on the evaluation and treatment of CS patients:

Patients have a relatively high frequency of occult AF detected when prolonged outpatient cardiac monitoring is performed similar to other prior studies^[3,4,13–15];

MOCHA panel elevation of ≥ 2 markers post-stroke was able to effectively predict patients that subsequently were diagnosed with occult AF suggesting that an underlying left atrial cardiopathy in these patients may contribute to a prothrombotic state detected by the MOCHA panel before the arrhythmia is ever detected;

given that non-cardiac causes such as occult malignancy can contribute to CS, a combination of cardiac markers such as the LAVI on TTE and non-cardiac markers such as the MOCHA panel will be more effective at identifying patients who may benefit from early anticoagulation than cardiac markers alone;

a normal MOCHA panel on antiplatelet therapy may identify a subgroup of CS patients who are unlikely to benefit from early anticoagulation.

We chose to evaluate the MOCHA panel in our study because CS is primarily thought to be mediated through a thromboembolic event. Because the four markers in the panel are associated with coagulation activation (PTF 1.2, TAT, FM) or fibrinolysis (DD), we anticipated that a persistent elevation in these tests beyond 2 weeks post-stroke would be a marker of an underlying coagulopathic state. Additionally, previous studies have shown the individual markers to be associated with elevations in AF, coronary artery disease, malignancy, and cardioembolic stroke.^[6–9]

All of our patients were placed on antiplatelet therapy after their CS based on current treatment guidelines, however, we chose these prespecified endpoints because they were considered indications that would prompt providers to switch patients from antiplatelet to anticoagulation therapy. Further, CS patients with abnormal MOCHA markers on antiplatelet therapy who were transitioned to anticoagulation after having an endpoint in the study had normalization of all of their markers suggesting that their hypercoagulable condition was suppressed with anticoagulation therapy. Given the recent cessation of the NAVIGATE-ESUS study with no benefit seen in CS patients placed on rivaroxaban 20 mg daily versus aspirin 325 mg daily,^[16,17] evaluation of biomarkers soon after stroke will be useful to identify patients who may require early anticoagulation in this trial and the other ongoing trials including RESPECT-ESUS^[18] and ATTICUS.^[19]

Our study has several limitations:

Our small sample size of CS patients who underwent MOCHA evaluation requires further validation in a larger cohort study; given that 38% of patients did not want to undergo ILR placement, we may have missed detection of occult AF in some of these patients;

our patients were all treated initially after their CS with antiplatelet therapy which may affect the generalizability of our recurrent stroke rates with other cohorts that allowed anticoagulation therapy.

In summary, abnormal MOCHA levels identified CS patients who were more likely to have a subsequent diagnosis of AF, malignancy or recurrent stroke during follow-up and may be complementary to LA structural abnormalities in identifying patients who could benefit from early anticoagulation. Given that normal MOCHA levels in CS patients on antiplatelet therapy had a 100% NPV for our composite outcome, the MOCHA panel may additionally identify a subgroup of patients who are unlikely to benefit from early anticoagulation. Evaluating MOCHA in a larger CS cohort is warranted.

Author contributions

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