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Assessment of Novel Biomarkers and CHA_2DS_2-VASc Score in Predicting Stroke and All-cause Death in Patients With and Without Atrial Fibrillation

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Abstract

Assessment of Novel Biomarkers and CHA_2DS_2-VASc Score in Predicting Stroke and All-cause Death in Patients With and Without Atrial Fibrillation

By Yunyun Chen

Objective: Given that patients with atrial fibrillation (AF) have an increase in stroke risk, CHA_2DS_2-VASc has been recommended by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines to manage AF. We considered five novel biomarkers, C-reactive protein (CRP), heat shock protein (HSP), fibrin degradation product (FDP), high sensitivity troponin, and soluble urokinase-type plasminogen activator receptor (suPAR) used in cardiovascular disease outcome prediction, to evaluate whether including these biomarkers improves the prediction performance for stroke and all-cause death.

Methods: A total of 383 adult patients with AF and 2,729 without AF were included in analysis, and all five biomarkers were collected at baseline. Proportional sub-distribution hazards models and Cox proportional hazards models were used to analyze the relationship between stroke, death and CHA_2DS_2-VASc score and five biomarkers for patients with and without AF. C-statistics, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to compare model prediction performance.

Results: When CHA_2DS_2-VASc changed from 0-1 to 6 or more, the cumulative incidence of stroke increased by 0.40 for those without AF at 2,500 days of follow-up. When predicting death, for one unit increase in CHA_2DS_2-VASc score, suPAR and FDP, the estimated hazard ratios were 1.28(95% CI=[1.16, 1.41]), 1.16(95% CI=[1.11, 1.21]) and 1.01(95% CI=[1.00, 1.02]). For patients without AF, with one unit increase in CHA_2DS_2-VASc score, suPAR and CRP, the estimated hazard ratios were 1.30(95% CI=[1.22, 1.35]), 1.20(95% CI=[1.17, 1.23]) and 1.01(95% CI=[1.00, 1.01]). The c-statistic improved significantly from 0.65(95% CI=[0.60,0.70]) to 0.71(95% CI=[0.66,0.76]) after adding suPAR and FDP for patients with AF, and improved from 0.63(95% CI=[0.58,0.69]) to 0.71(95% CI=[0.65,0.76]) after adding suPAR and CRP for patients without AF.

Conclusions: Our results suggest that CHA_2DS_2-VASc score, suPAR and FDP were significantly associated with all-cause death in patients with AF and CHA_2DS_2-VASc score, suPAR and CRP were significantly associated with all cause death in patients without AF. The models incorporating these biomarkers can refine the prediction probability. More research is needed to validate our results.

Assessment of Novel Biomarkers and CHA_2DS_2-VASc Score in Predicting Stroke and All-cause Death in Patients With and Without Atrial Fibrillation

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Contents

1. Introduction

1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common type of irregular heartbeat and is an important public health issue nowadays. The prevalence was 2% among adults in Europe in 2014 (and higher among older men), which almost doubled when compared with the rate a decade ago [1]. AF is predicted to affect 6-12 million people in the U.S. by 2050 [2]. The common risk factors for AF include hypertension and valvular heart disease. The most common symptom for AF is a fluttering heartbeat. Other common symptoms include fatigue, irregular heartbeat, dizziness and chest pain.

1.2 Connection with Stroke

Many studies have shown that AF is a strong independent risk factor for having a stroke [3]. With AF, patients are approximately five times more likely to have a stroke [1]. In general, patients with AF-related stroke have a worse prognosis that includes longer hospitalizations, and higher in-hospital mortality, compared to those without AF [4]. Most patients who suffer from severe stroke are less likely to live for more than one year. On the other hand, long-term stroke survivors typically have serious disabilities and their quality of life is seriously affected.

Given that AF is known to increase the risk of stroke, it is critical to predict and manage the risk of stroke for patients with AF. Based on a precise risk prediction algorithm, appropriate treatment or prevention strategies can be applied to reduce stroke incidence and/or disabilities resulting from stroke. For instance, if we can predict the

risk accurately and identify patients with high risks of stroke, reliable guidance can be provided by clinicians to prescribe antithrombotic therapy in advance [5]. Risk stratification schemes may also be very useful for the management of patients who already have had a stroke [5].

1.3 Existing Risk Scores for Predicting Stroke after Atrial Fibrillation

Atrial Fibrillation Investigators (AFI 1994) used increasing age, history of hypertension, previous transient ischemic heart attack or stroke and diabetes as risk factors for stroke [6]. Robert G. Hart (1999, SPAF investigators) showed age, female sex, history of hypertension, systolic blood pressure>160 mmHg and prior stroke or transient ischemic heart attack were independently associated with increased stroke risk [3]. Gage BF (2004) used $CHADS_2$ scheme, which includes congestive heart failure, hypertension, age≥75, diabetes mellitus and prior stroke or transient ischemic heart attack to successfully identify patients who are at high risk of stroke [5]. The Framingham Heart Study (2003) used advancing age, female sex, increasing systolic blood pressure, prior stroke or transient ischemic heart attack and diabetes to derive a risk score for stroke [6]. The National Institute for Health and Clinical Excellence (NICE) guidelines (2006) used age >65 or age >75, hypertension, diabetes, vascular disease and clinical evidence of valve disease or heart failure, or impaired left ventricular function as risk score factors [7]. The ACA/AHA/ESC guidelines (2006) used age≥ 75, hypertension, heart failure, left ventricular ejection fraction (LVEF) ≤35%, diabetes, previous stroke, transient ischemic attack (TIA) or embolism as risk factors [8]. The American College of Chest Physicians (ACCP 2008) used age,

hypertension, moderately or severely impaired LVEF, heart failure, diabetes mellitus, previous stroke, TIA, or having an embolism as risk factors to derive risk scores [9]. Birmingham (2009) used congestive heart failure or impaired LFEV, hypertension, age≥ 75, diabetes mellitus, stroke or TIA or thromboembolism (TE), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65-74 years old and sex as risk factors, with the acronym CHA_2DS_2-VASc [10]. Now CHA_2DS_2-VASc has been recommended by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines to manage AF.

1.4 Limitations of Existing Risk Scores

Although the American College of Chest Physicians (ACCP) and Canadian Cardiovascular Society guidelines recommended the $CHADS_2$ score [11][12], the $CHADS_2$ score may not categorize patients precisely into truly low risk of stroke [13]. When patients are categorized into different risk levels, they are treated differently. For example, when a patient's $CHADS_2$ score equals 1, he/she does not need to be treated with anticoagulation. When calculating the CHA_2DS_2-VASc score for the same patient, the score may be greater than two because more risk factors are considered in CHA_2DS_2-VASc. This means oral anticoagulation is needed [14]. Thus, for patients with $CHADS_2$ scores less than two, utilization of risk stratification by applying CHA_2DS_2-VASc is needed [14].

CHA_2DS_2-VASc score has been used in the European Society of Cardiology [15] and can better identify truly low-risk patients compared to $CHADS_2$ [10]. Most importantly, fewer patients are regarded as intermediated risk, which offers significant aid to clinical decision making. In other words, physicians do not need to choose aspirin or oral anticoagulant treatment [16]. However, CHA_2DS_2-VASc has a low specificity and tends to classify more patients as high risk. Patients with high risk of stroke usually are treated with long-term anticoagulants. This may expose them to unnecessary bleeding risk [16].

1.5 Novel Biomarkers for Cardiovascular Disease

C-reactive protein (CRP), heat shock protein (HSP), fibrin degradation product (FDP), high sensitivity troponin, and soluble urokinase-type plasminogen activator receptor (suPAR) are known to be related to cardiovascular disease. CRP is an annular, pentameric protein found in blood plasma, whose levels rise in response to inflammation [17]. CRP concentration is associated with the risk of coronary heart disease and ischemic stroke [18]. HSP is a family of proteins that are produced by cells in response to exposure to stressful conditions [19]. HSP has a protective effect in AF in many cardiomyopathy conditions [20]. Fibrin degradation product is a component of the blood produced by clot degeneration [21]. The primary degradation product of cross-linked fibrin is D-dimer and it is associated with the risk of a future myocardial infarction [22]. High sensitivity troponin-I (hs-TnI) level is associated with risk of stroke and by adding hs-TnI levels to CHA_2DS_2-VASc score, the c-statistic for stroke prediction has been shown to improve [23]. suPAR is a marker of disease severity and

aggressiveness [24]. Moreover, it is associated with an increased incidence of ischemic stroke [25]. Given that these five biomarkers are strongly associated with cardiovascular disease, we investigated their contributions to stroke prediction and their ability to refine current risk scores.

1.6 Study Goals

All of the existing risk scores prediction methods are useful for predicting risk of stroke in patients with AF. However, they may not give accurate predictions in certain scenarios or sub-groups. For example, $CHADS_2$ cannot predict risk accurately for truly low risk patients. And both $CHADS_2$ and CHA_2DS_2-VASc have limited ability to predict stoke in patients with AF for Taiwanese compared to Western patients[26]. The prediction ability of one year prognosis of stroke is also limited for Chinese patients with non-valvular atrial fibrillation (NVAF) [27]. The purpose of this study was to develop a novel risk score algorithm for stroke and all-cause mortality based on the CHA_2DS_2-VASc while incorporating the aforementioned five biomarkers.

1.7 Significance

With the novel risk score, risk of stroke in patients with AF can be better predicted. Then appropriate treatments can be used for these patients and disabilities resulting from stroke can be reduced.

2. Methods

2.1 Study Population

Our study patients came from a subset of the Emory Cardiology Biobank, which was established to investigate the genetic basis of oxidative stress, vascular dysfunction, cardiovascular disease and stroke [28]. Specifically, our analysis sample consists of a total of 383 adult patients (aged 18 years or older) with AF and 2,729 without AF enrolled in the Biobank prior to undergoing cardiac catheterization across three Emory Healthcare sites, between 2004 and 2015. Various clinical variables were collected at enrollment, including age, race, medical history (including history of hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, heart failure and prior myocardial infarction), treatment history (including use of angiotensin receptor blockers (ARBs) inhibitor / angiotensin converting enzyme (ACE) inhibitor, use of aspirin and statins). In addition, the levels of the five biomarkers of interest, CRP, HSP, FDP, high sensitivity troponin and suPAR, were also recorded. Furthermore, information about whether patients developed stroke or not and the time to stroke (in days) was also gathered. For patients who died during the follow up, the date of death was collected as well.

The Institutional Review Board at Emory University, Atlanta, GA, USA approved the study. All patients agreed to be enrolled in the study.

2.2 CHA_2DS_2-VASc Score Calculation

According to CHA_2DS_2-VASc score, patients were given 1 point for congestive heart failure or left ventricular dysfunction, hypertension, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age

65-74 years and female. They were given 2 points for age older or equal to 75 years and stroke or TIA or TE. These were all calculated based on baseline characteristics.

2.3 Statistical Analysis

2.3.1 Descriptive Analysis

Continuous variables were summarized as mean ± standard deviation (SD). Given the skewed distribution of the five biomarkers, they were summarized using median and lower and upper quartiles. Categorical variables were summarized using counts and percentages.

2.3.2 Univariate Analysis

Baseline characteristics were compared between patients with AF and those without using the chi-square test for categorical variables and the two sample t-test for continuous variables. The Wilcoxon rank sum test was used to test the differences in the five biomarkers between the two groups.

2.3.3 Model Assessment

Prior to fitting a Cox proportional hazard model, we calculated the cumulative martingale residuals to check the function form of each variable. Martingale residuals are the difference between observed number of events and the expected numbers according to fitted model for a specific individual. The plot for cumulative martingale residuals is a partial-sum process of the residuals and can be used to see how unusual the observed process is under the model [29]. Variable transformation needs to be considered if the pattern of the plot is unusual. In our study, each continuous biomarker

was added in the Cox model with stroke as the outcome separately. According to the Kolmogorov-type supremum test based on a sample of 1,000 simulated residual patterns, the p-values for high sensitivity troponin, suPAR, CRP, FDP and HSP were all larger than 0.05, thus we treated all biomarkers as continuous variables for analysis.

2.3.4 Multivariable Analysis

Separate models were used to analyze the relationship between time to stroke and other explanatory variables including CHA_2DS_2-VASc score, CRP, HSP, FDP, high sensitivity troponin and suPAR for patients with and without AF. As death was the competing risk for stroke, the extension of the Cox regression (proportional sub-distribution hazards model) developed by Fine and Gray [30], was used. When death was regarded as the outcome, the Cox model was used to analyze the relation between death and CHA_2DS_2-VASc score, CRP, HSP, FDP, high sensitivity troponin and suPAR. The final model contained all significant biomarkers.

2.3.5 Model Prediction Performance Metrics

To compare the clinical model with only CHA_2DS_2-VASc score and the model with significant biomarkers, Uno methods for c-statistics [31] and Uno and Tianxi Cai's methods for continuous net reclassification improvement (NRI) /integrated discrimination improvement (IDI) [32] were used. C-statistics can be used to measure concordance between observed and model-based risk [33]. It is the probability that the model predicts a higher risk for individuals who experienced an event than those who did not [33]. A c-statistic of 1 represents perfect discrimination. When it is greater than

0.7, the model is considered reasonable [34]. In a setting of binary outcome, the c-statistic equals the area under the receiver operating characteristic (ROC) curve, which is a plot of sensitivity vs 1 minus specificity [33]. An R package **survC1** was used to calculate c-statistics for each model and compare the difference in c-statistics between models. NRI and IDI can be used to evaluate predictive improvement in reclassification for models with censored survival data by comparing two risk prediction models. NRI sums up two parts, one for patients with event and other for patients without events. For those with event, 1 is assigned if they have upward reclassification, -1 for downward and 0 for those not change. For patients without event, the score will be assigned oppositely. Then the total sum score is divided by the number of people in each group. An R package **survIDINRI** was used to calculated NRI and IDI.

All statistical analysis was conducted using SAS 9.4 (Cary, NC) and R 3.2.2. P-values less than 0.05 were considered statistically significant.

3. Results

3.1 Patient Characteristics

The study population comprised 3,112 patients with a median follow-up time of five years. A total of 383 patients (12.3%) had a diagnosis of AF at baseline. Baseline characteristics of these patients are presented in Table 1. Forty-nine (12.8%) and 189 (6.9%) patients with and without AF had a stroke history, respectively. There were significant differences in gender, age, race, heart failure and prior stroke for patients with and without AF. The group of patients with AF had fewer women, fewer African Americans, more people with heart failure and stroke at baseline than the group without

AF. Patients with AF were older and had higher biomarker levels than the patients without AF.

The distributions of CHA_2DS_2-VASc scores in the study population stratified by presence of AF are shown in Table 2. A total of 20 (5.2%) patients with AF and 79 (2.9%) patients without AF developed stroke during the follow-up period. Forty percent of the patients with AF had a CHA_2DS_2-VASc score from 2 to 3 while 47.4% of the patients without AF were in this score range. Forty percent of the patients with AF and 41.8% without AF developed stroke had a CHA_2DS_2VASc score from 4 to 5. Forty-two percent of the patients with AF died during follow-up had CHA_2DS_2-VASc scores from 4 to 5 while 39.7 % of the patients without AF died had CHA_2DS_2-VASc scores from 2 to 3.

3.2 Association between CHA_2DS_2-VASc and Stroke

We did not find significant an association between CHA_2DS_2-VASc and time to stroke in patients with AF, possibly due to the small number of events in our data. On the other hand, for patients without AF, CHA_2DS_2VASc was a significant predictor for stroke ($p < 0.0001$). Figure 1 shows the cumulative incidence functions for stroke among patients with various CHA_2DS_2-VASc scores. When CHA_2DS_2-VASc changed from 0-1 to 6 or more, the cumulative incidence of stroke increased by 0.40 for those without AF at 2,500 days of follow-up. The findings confirmed that the CHA_2DS_2-VASc was sensitive and useful for stroke risk prediction in patients without AF. However, none of the five biomarkers was found to be significantly associated with stroke (when considering death as a competing risk).

3.3 All-cause Death

Table 3 shows the results of the Cox models when death was treated as the outcome. For patients with AF, CHA_2DS_2-VASc score, suPAR and FDP were significant for predicting death. For one unit increase in CHA_2DS_2VASc score, suPAR and FDP, the estimated hazard ratios were 1.28(95% CI=[1.16, 1.41]), 1.16(95% CI=[1.11, 1.21]) and 1.01(95% CI=[1.00, 1.02]). For patients without AF, -VA CHA_2DS_2Sc score, suPAR and CRP were significant for predicting death. For one unit increase in CHA_2DS_2Sc -VASc score, suPAR and CRP, the estimated hazard ratios were 1.30(95% CI=[1.22, 1.35]), 1.20(95% CI=[1.17, 1.23]) and 1.01(95% CI=[1.00, 1.01]). We found that suPAR was useful for predicting death for both AF and non-AF groups.

Figure 2 shows the cumulative incidence functions for patients with various CHA_2DS_2-VASc scores using death as the outcome including significant covariates. When CHA_2DS_2-VASc changed from 0-1 to 6 or more, the cumulative incidence of death increased by 0.05 for patients with AF and 0.37 for those without AF at 2,500 days of follow-up, respectively.

3.4 Model Prediction Performance

Table 4 shows the prediction performance metrics of the above survival models, including the c-statistic, continuous NRI and IDI. For patients with AF, the c-statistic for the model with CHA_2DS_2-VASc score only was 0.65(95% CI=[0.60,0.70]). The c-statistic improved significantly to 0.71(95% CI=[0.66,0.76]) after adding suPAR and FDP to the model. For patients without AF, the c-statistic for the model with CHA_2DS_2-

VASc score only was 0.63(95% CI=[0.58,0.69]). The c-statistic improved significantly to 0.71(95% CI=[0.65,0.76]) after adding suPAR and CRP. Thus, by adding biomarkers to the model, the prediction performance was improved.

4. Discussion

4.1 Results

Even though we did not find CHA_2DS_2-VASc score to be useful for predicting stroke in our 383 patients with AF, it is significantly associated with stroke in patients without AF. On the other hand, the CHA_2DS_2-VASc score is useful for predicting death. Among the five biomarkers, only suPAR was associated with death for patients with and without AF. FDP was associated with death for patients with AF and CRP was associated with death for patients without AF. In terms of model prediction performance, adding new biomarkers better predicted death risk compared to the model with CHA_2DS_2-VASc score only.

4.2 Previous Study

A previous study reported significant association between CHA_2DS_2-VASc score and risk of ischemic stroke for patients with heart failure with and without AF [35]. When predicting death, the results of our study were similar with the previous study in showing that CHA_2DS_2-VASc score could be used to predict death [35]. Our findings with regards to biomarkers are consistent with previous studies. In a prospective study, Eugen-Olsen et al. found that risks of cancer, CVD and mortality increase with suPAR levels in Caucasians [36]. FDP has been shown to be a strong predictor of death and

myocardial infarction [37]. The Emerging Risk Factors Collaboration showed associations between CRP and vascular mortality and death from cancers [18]. Our study verified these results.

4.3 Limitations

Unfortunately, the sample size of patients with AF and the number of stroke events in our study were small. Hence, the prediction ability of CHA_2DS_2-VASc score was inconclusive and was inconsistent when compared to previous studies. We also did not find significant associations between biomarkers and stroke, which needs further investigations in larger cohorts. In addition, all the study patients were from the Emory Cardiovascular Biobank database, so the findings may not be generalized to other populations. Another limitation was related to the uncertainty of AF status at enrollment. In fact, up to 25% of the AFs were silent, and a study showed that patients without AF may actually have undiagnosed AF [38]. Moreover, patients may develop AF during the follow-up period. Lastly, we were unable to account for anticoagulation treatments due to lack of data. Some patients with high CHA_2DS_2-VASc scores may have been treated with anticoagulation by the time of enrollment, thereby significantly reducing their risks of developing stroke.

4.4 Future Research

To validate the results of our study, independent cohort studies with more patients with and without AF and patients from other hospitals in the U.S. or other countries are needed. Additionally, a longitudinal study with regular follow-ups collecting patient's

medical information including change of AF status, treatment, and biomarker levels can be extremely useful for the development of a dynamic prediction algorithm for stroke or death. This risk prediction algorithm has the potential to provide real-time information to guide AF management.

4.5 Conclusions

Our results suggest that CHA_2DS_2-VASc score, suPAR and FDP were significantly associated with all-cause death in patients with AF and CHA_2DS_2-VASc score, suPAR and CRP were significantly associated with all-cause death in patients without AF. The models incorporating these biomarkers can refine the prediction probability. More research is needed to validate our results.

Table 1 Baseline Characteristic of the Stroke Biomarkers Stratified According to Prior Diagnosis of Atrial Fibrillation

	No. (%) of Patients		
	Atrial Fibrillation	No Atrial Fibrillation	p-value
Baseline Characteristics	(n=383)	(n=2729)	
Female	107(27.9)	1007(36.9)	<0.001
Age at baseline, mean (SD)	69.13(10.6)	62.61(11.3)	<0.001
Race			<0.001
Caucasian White	338(88.3)	2176(79.7)	
African American	39(10.2)	528(19.3)	
Other	6(1.5)	35(1.0)	
History of Hypertension	232(60.6)	1602(58.7)	0.486
History of Diabetes Mellitus	109(28.5)	7893(32.7)	0.094
Coronary Artery Disease	234(61.1)	1591(58.3)	0.298
Peripheral Artery Disease	24(6.3)	227(8.3)	0.167
Heart Failure	138(36.0)	439(16.1)	<0.001
Prior Stroke	49(12.8)	189(6.9)	<0.001
Prior Myocardial Infarction	129(33.7)	856(31.4)	0.362
ARBs/ACE inhibitors Use	267(69.7)	1734(63.5)	0.018
Aspirin Use	301(78.6)	2207(80.9)	0.290
Statin Use	276(72.1)	1977(72.4)	0.876
High sensitivity troponin (pg/Ml), median (Q_1,Q_3)	8.9(4.5, 26.1)	5.1(2.8, 13.6)	<0.0001
Heat shock protein 70 (ng/Ml), median (Q_1,Q_3)	0(0, 1)	0(0,0)	0.0015
Fibrin degradation product (ug/Ml), median (Q_1,Q_3)	0.6(0.4, 1.0)	0.54(0.4, 0.8)	0.0050
suPAR (ng/Ml), median (Q_1,Q_3)	3.4(2.7, 4.6)	2.98(2.3, 3.9)	<0.0001
C-reactive protein (mg/Dl), median (Q_1,Q_3)	3.1(1.3, 8.2)	3(1.2, 7.5)	0.2134

ARBs inhibitors: Angiotensin Receptor Blockers inhibitor

ACE inhibitors: angiotensin converting enzyme(ACE) inhibitor

suPAR: soluable urokinase-type plasminogen activator receptor

Table 2 Baseline CHA_2DS_2-VASc Scores and Number of Events Stratified According to Prior Diagnosis of Atrial Fibrillation

		No. (%) of Patients					
		Atrial Fibrillation (n=383)	Stroke (n=20)	Death (n=133)	No Atrial Fibrillation (n=2729)	Stroke (n=79)	Death (n=459)
CHA_2DS_2-VASc							
	0,1	70(18.28)	3(15)	9(6.77)	735(26.93)	8(10.13)	55(11.98)
	2,3	154(40.21)	7(35)	44(33.08)	1295(47.45)	28(35.44)	182(39.65)
	4,5	113(29.50)	8(40)	56(42.11)	576(21.11)	33(41.77)	167(36.38)
	≥ 6	46(12.01)	2(10)	24(18.04)	123(4.51)	10(12.66)	55(11.98)

Table 3 Cox Model Estimates for Patients with and without Atrial Fibrillation for Death Outcome

Atrial Fibrillation		No Atrial Fibrillation	
	HR (95% CI)		HR (95% CI)
CHA_2DS_2-VASc	1.28(1.16,1.41)	CHA_2DS_2-VASc	1.30(1.22,1.35)
suPAR (ng/mL)	1.16(1.11,1.21)	suPAR (ng/mL)	1.20(1.17,1.23)
FDP (ug/mL)	1.01(1.00 1.02)	CRP (mg/dL)	1.01(1.00,1.01)

suPAR: soluable urokinase-type plasminogen activator receptor

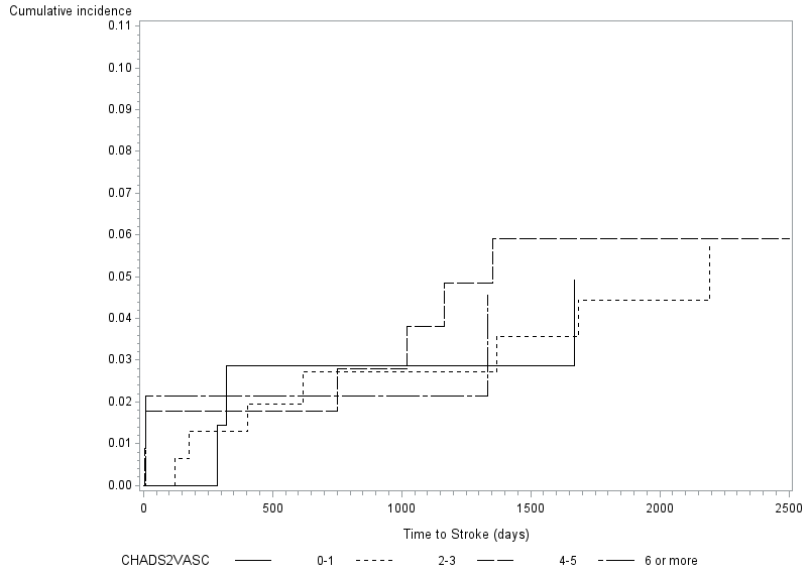
FDP: fibrin degradation product

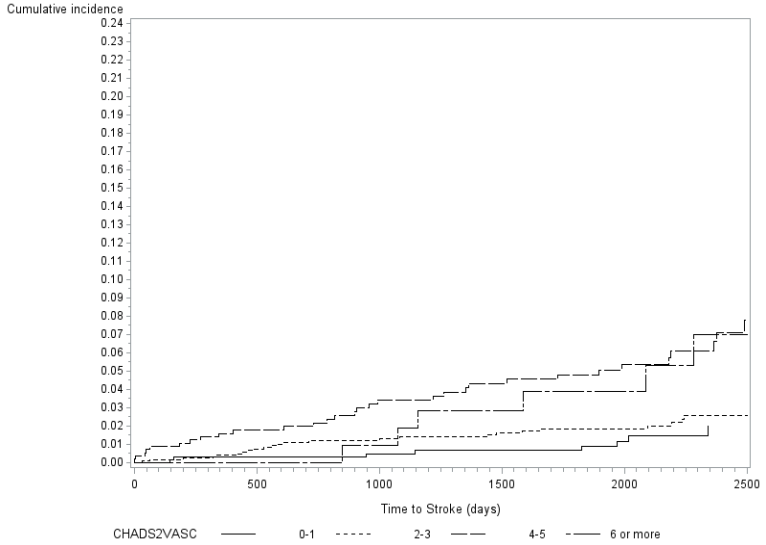
CRP: C-reactive protein

Table 4 Compare Models with and without Biomarkers by Using Death as the Outcome

	C-statistics	95% CI	ΔC-statistics	95% CI	IDI	95% CI	NRI	95% CI
Atrial Fibrillation								
Model0	0.65	(0.60,0.70)						
Model1	0.71	(0.66,0.76)	0.06	(0.03,0.09)	0.12	(-0.01,0.29)	0.49	(-0.12,1.14)
No Atrial Fibrillation								
Model0	0.63	(0.58,0.69)						
Model1	0.71	(0.66,0.76)	0.08	(0.03,0.12)	-0.01	(-0.04,0.02)	-0.52	(-0.74, -0.16)

For patients with Atrial Fibrillation, Model0 represents the model just with CHA_2DS_2-VASc score. Meodel1 represents CHA_2DS_2-VASc score, suPAR and FDP. For patients without Atrial Fibrillation, Model0 represents the model just with CHA2DS2-VASc score. Meodel1 represents CHA2DS2-VASc score, suPAR and CRP.

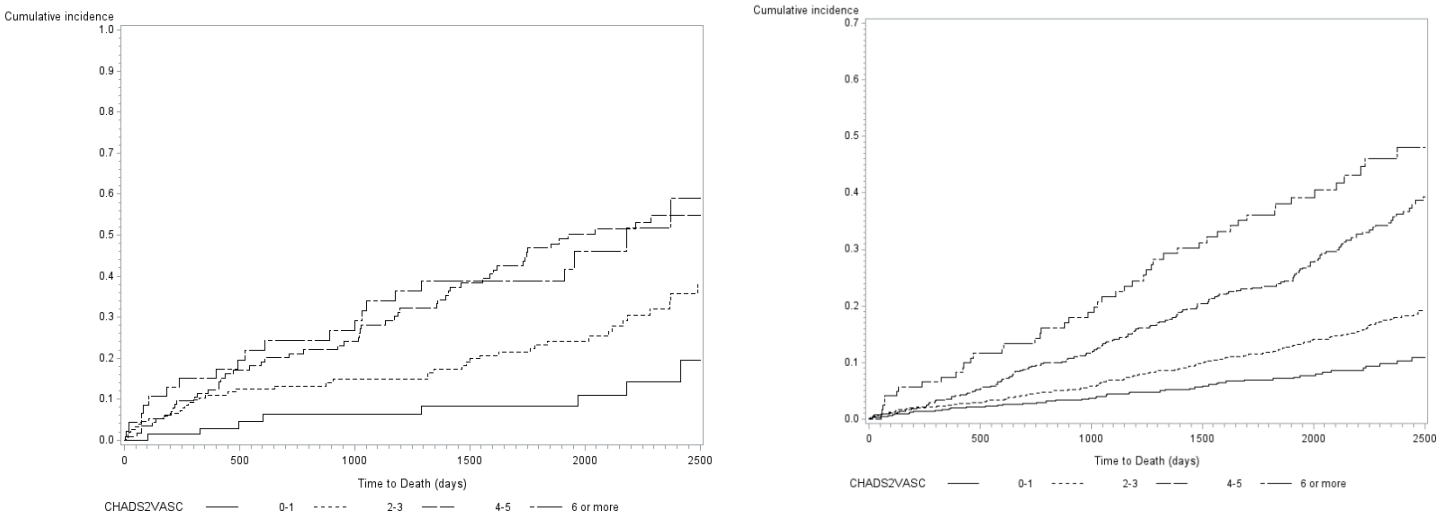




Atrial Fibrillation

No Atrial Fibrillation

Figure 1. Cumulative Incidence Functions for Patients with and without Atrial Fibrillation Categorized by CHA_2DS_2-VASc Treating Stroke as the Outcome



Atrial Fibrillation

No Atrial Fibrillation

Figure 2. Cumulative Incidence Functions for Patients with and without Atrial Fibrillation Categorized by CHA_2DS_2-VASc Treating Death as the Outcome

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