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A circulating biomarker risk-prediction model correlates with CHADS-2 risk score in chronic atrial fibrillation☆,☆☆

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ABSTRACT

Background: Inflammation and oxidative stress have been linked to the origin and persistence of atrial fibrillation (AF). CHADS-2 scoring system is a risk stratification schema well validated in prognostication of stroke in AF. We evaluated the association of markers of oxidative stress and inflammation with CHADS-2 scores in chronic AF patients.

Methods: CHADS-2 scores were calculated for 64 subjects with chronic AF. Serum markers of inflammation [C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α)] and of oxidative stress [derivatives of reactive oxygen metabolites (DROMs) and isoprostanes (IsoPs)] were measured.

Results: Twenty subjects were categorized as 0 (no risk), 24 as 1 (intermediate risk) and 20 as 2 (severe risk) based on their CHADS-2 scores. High sensitivity-CRP (CHADS-2 0 = 40.0%, 1 = 70.0%, 2 = 90.0%; $p = 0.003$) and DROMs (CHADS-2 0 = 45%, 1 = 78%, 2 = 80%; $p = 0.04$) were positively associated with the CHADS-2 risk score. Subjects with intermediate to severe CHADS-2 risk retained significant associations with abnormal hs-CRP (OR: 5.3, 95%CI: 1.1–25.0) and DROMs (adjusted OR: 6.7, 95%CI: 1.2–38.8) after adjusting for gender and hypertension. In a multiple logistic interaction model, there was no significant interaction between hs-CRP and DROMs in their association with CHADS-2 risk categories ($p = 0.64$). A biomarker risk-model, combining hs-CRP and DROMs, correlated well with the CHADS-2 risk categories ($r = 0.49$, $p < 0.001$).

Conclusions: A biomarker risk-model using a combination of hs-CRP and DROMs correlates well with CHADS-2 risk scores in chronic AF. Either or both of these markers may add predictive power to future stroke risk prediction models.

1. Introduction

Stroke is the most debilitating complication of chronic atrial fibrillation (AF) [1,2]. Major risk factors for stroke include a history of a prior stroke or transient ischemic attack (TIA), presence of hypertension or diabetes, age > 75 years, and poor left ventricular function [2]. Long term anticoagulation helps prevention of this drastic complication of chronic AF [3]. The chronic use of anticoagulation involves consideration of associated risks of life threatening bleeding [4]. Several risk stratification scoring schemes [5,6] have been developed to determine which patients with chronic AF have the highest stroke risk and, thus, would benefit the most with chronic anticoagulation. Most widely used among these is the CHADS-2 risk score [5], where C stands for congestive heart failure, H for hypertension, A for age greater than or equal to 75 years, D for diabetes and S for prior strokes or TIAs. Each of the factors assigns 1 point except for history of TIA or stroke that adds 2 points. Adjusted stroke rate per 100 patient-years increases as the CHADS-2 scores increase [5]. Recently, the CHADS-2 score has been supplemented with a modified CHADS-2 Vasc score which also includes the presence of vascular disease and adds an extra point for age >75 years [7]. These risk stratification schemas help in determining

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Table 1
Baseline clinical characteristics of the study population.

Variables	CHADS-2 risk categories			*P*-value
	Low risk (0)	Intermediate risk (1)]	Severe risk (2 or higher)	
Age (years)	60.0 ± 7.4	57.6 ± 12.4	59.9 ± 17.0	0.8
Males (%)	90.0%	91.7%	65.0%	**0.04**
Whites (%)	95.0%	87.5%	70%	0.09
BMI (kg/m^2)	32.0 ± 9.1	34.4 ± 12.2	34.6 ± 14.8	0.8
Smokers (%)	30.0%	20.8%	10.0%	0.3
HTN (%)	5.3%	75.0%	65.0%	<**0.001**
Diabetes (%)	5.0%	4.3%	20.0%	0.1
Coumadin (%)	90.0%	91.7%	85.0%	0.8

A CHADS-2 score was calculated for each subject by assigning one point each for age >75 years, hypertension, diabetes and heart failure or low ejection fraction, and two points for history of prior stroke or TIA.

the need for anticoagulation therapy in patients with chronic AF and guide physicians in management. Nevertheless, there remains a need for a refinement in risk prediction models, especially in patients who fall in the low to intermediate or intermediate risk category on these risk scores.

Inflammation has been linked to the chronicity of AF and its thrombo-embolic complications [8]. C-reactive protein (CRP), a marker of inflammation, has been associated persistence and recurrence of AF as well as with the incidence of stroke [9]. Recently, markers of systemic oxidative stress have been associated with AF [10]. Higher levels of the derivatives of reactive oxygen species (DROMs) and F2-isoprostanes (IsoPs) are found in patients with persistent AF compared to age-matched controls [10]. In an animal model, there is evidence of loss of the antiplatelet agent, nitric oxide, and of endocardial dysfunction in the left atrium and left atrial appendage during AF [11,12]. Nevertheless, it is unknown if elevated levels of these markers are also associated with stroke risk in AF. We aimed to determine if the levels of markers of oxidative stress and inflammation correlated with CHADS-2 risk score in patients with chronic atrial fibrillation.

2. Methods

Consecutive subjects with electrocardiographically (ECG) documented chronic AF were enrolled from clinics at the Atlanta Veterans Affairs Medical Center and Emory University Affiliated hospitals during years 2004–2006 (NCT00252967). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. All subjects provided written informed consent. AF was defined as the absence of P waves and irregular RR intervals on ECG. Chronic AF was defined as persistent AF for more than a year. Exclusion criteria included age <18 years, paroxysmal AF, hemodynamic instability, thyroid disorders, uncontrolled hypertension (blood pressure > 180/100 at rest), presence of inflammatory condition or malignancies. Medical records were reviewed for baseline demographic and clinical data including presence of cardiovascular disease, hypertension, and diabetes, history of strokes or TIAs, left ventricular systolic function and concomitant medications.

A CHADS-2 score was calculated for each subject by assigning one point each for age >75 years, hypertension, diabetes and heart failure or low ejection fraction, and two points for history of prior stroke or TIA. Hypertension was defined either by historical documentation, readings obtained of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Diabetes was present if reported by a physician or the patient was using anti-diabetic agents and/or insulin. The presence of heart failure was determined either from the medical records or by an ejection fraction of less than 50% on a recent echocardiogram. History of stroke or TIA was determined from the medical records.

Plasma levels of markers of inflammation and oxidative stress were measured in a non-fasting state. Abnormal levels were defined using the upper limit of normal reference range as a cut off. (TNF-α < 8 pg/mL; IL-6 < 5 pg/mL; IL-1 < 3 pg/mL; hs-CRP < 3 mg/L; DROM 250–300 Carr Units; Isoprostanes 351–685 pg/mL). Markers of oxidative stress included IsoPs and DROMs. Concentration of DROMs was determined using spectrometry (505 nm) [13]. IsoPs were quantified by gas chromatography/mass spectrometry [14]. Systemic inflammatory markers [hs-CRP, interleukin-6 (IL-6), interleukin 1β (IL-1β), and tumor necrosis factor-α (TNF-α)] were measured using commercially available assays.

Categorical variables were compared using Chi-square tests while continuous variables were compared using analyses of variance. Multiple logistic regression models were used to analyze independent associations of DROMs and hs-CRP with CHADS-2 risk categories. An interaction model was used to evaluate covariance between hs-CRP and DROMs in their association with CHADS-2 risk categories. A biomarker risk model was constructed giving a score of 1 for each abnormal DROMs or hs-CRP value, and this was correlated with CHADS-2 risk scores.

3. Results

Sixty-four subjects were enrolled. Based on their CHADS-2 scores, 20 subjects were categorized as 0 (no-risk), 24 as 1 (intermediate-risk) and 20 as 2 (severe-risk). Subjects in the three risk categories were similar in mean age ($p = 0.83$), smoking status ($p = 0.29$) and diabetes ($p = 0.14$), but differed in gender distribution ($p = 0.04$) and hypertension ($p < 0.001$) (Table 1). CHADS-2 risk categories significantly differed in having abnormal hs-CRP (0 = 40.0%, 1 = 70.0%, 2 = 90.0%; $p = 0.003$) and DROMs (0 = 45%, 1 = 78.3%, 2 = 80%; $p = 0.04$). No difference was found in IL-1β, IL-6, TNF-α and IsoPs (Fig. 1). Subjects with intermediate to severe CHADS-2 risk retained significant association with abnormal hs-CRP (OR: 5.3, 95%CI: 1.1–25.0) and DROMs (adjusted OR: 6.7, 95%CI: 1.2–38.8) after adjusting for gender and hypertension. There was no significant interaction between hs-CRP and DROMs in their association with CHADS-2 risk categories in multiple logistic interaction model ($p = 0.64$) (Fig. 2). A biomarker risk model, combining hs-CRP and DROMs, correlated well with the CHAD-2 risk categories ($r = 0.49$, $p < 0.001$).

4. Discussion

In our study, plasma levels of hs-CRP, a marker of inflammation, and DROM, a marker of oxidative stress, correlated well with the CHADS-2 risk score in patients with chronic AF. In addition, the combination of the two biomarkers, i.e. hs-CRP and DROM, correlated better with CHADS-2 score than either one alone. Though the correlation of CHADS-2 score with plasma hs-CRP has previously been shown [15],

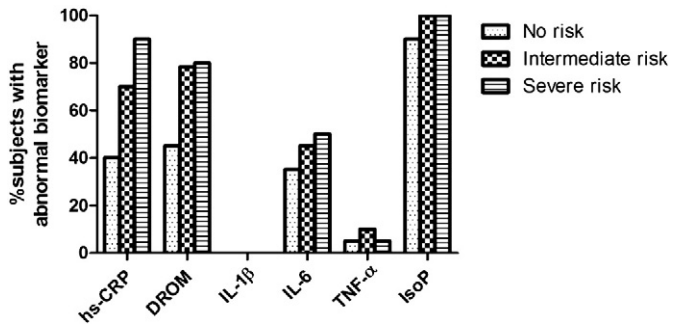

Fig. 1. Abnormal plasma levels of biomarkers of oxidative stress and inflammation across risk categories by CHADS-2 scores (hs-CRP, high sensitivity C-reactive protein; DROM, derivatives of reactive oxygen metabolites; IL-1β, interleukin Iβ; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; Iso-P, isoprostanes).

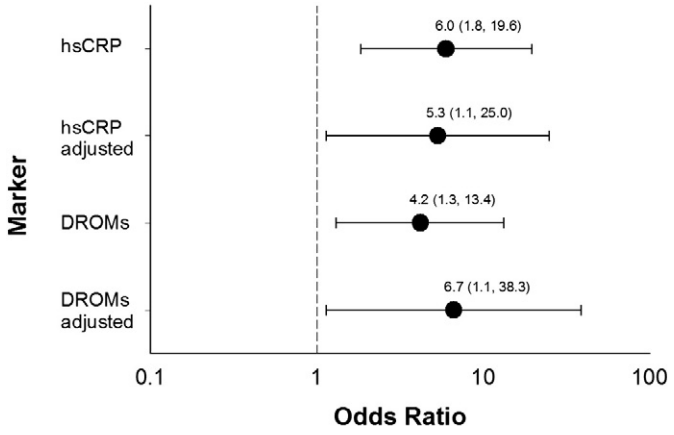

Fig. 2. Univariate and multivariate adjusted odds ratios of elevated hs-CRP and DROMs in the intermediate and high risk CHADS-2 risk score categories (hs-CRP, high sensitivity C-reactive protein; DROMs, derivatives of reactive oxygen metabolites).

this is the first study to show the correlation of this score with DROMs and the combination of the two biomarkers. The findings serve as indirect evidence in support of the causal association of inflammation and oxidative stress in the chronicity and thrombogenecity seen with AF.

C-reactive protein has been associated with chronicity in AF [16]. Studies have shown that levels of CRP correlate with inflammation, fibrosis, and remodeling [17]. In addition, CRP has also been associated with all-cause mortality and stroke in AF [18–20]. Possibly explaining the association, the inflammatory milieu is pro-coagulant and contributes to the thromboembolic complications in chronic AF [21].

Oxidative stress plays an important role in the pathogenesis and chronicity of AF [14,22,23]. Several redox signaling pathways have been described in AF that increase oxidative stress such as increased NADPH oxidase activity, nitric oxide synthase uncoupling and upregulation of xanthine oxidase [24–26]. Increased reactive oxygen species cause electrical, chemical and structural changes in AF, leading to chronicity and remodeling. In addition, there is activation of NF-κB and peroxisome proliferator-activated receptor and upregulation of plasminogen activator inhibitor-1, an important pro-thrombotic molecule, in response to oxidative stress [27]. This explains that the association of markers of oxidative stress does correlate with athero-embolic risk in chronic AF.

4.1. Study limitations

Our study has limitations. Firstly, the small sample size may have masked the correlation of other markers of inflammation and oxidative stress with CHADS-2 score. Nevertheless, we were able to show a statistically significant correlation of both hs-CRP and DROMs, and these markers with high discriminatory value are likely to be useful to improve stroke risk prediction models. Secondly, our study was cross-sectional and did not measure stroke risk prospectively. Future studies will need to determine any added value of these biomarkers to the current risk prediction scheme in a prospective manner with stroke as a primary outcome. Moreover, since we only looked at chronic AF patients, these markers may not be predictive in paroxysmal AF.

In conclusion, both hs-CRP and DROM levels were independently associated with CHAD-2 risk score. A biomarker risk-prediction model combining hs-CRP and DROM correlates well with CHAD-2 risk score and may be clinically useful for risk prediction in the setting of chronic AF. A combination of the biomarkers of inflammation and oxidative stress in the form of a risk-prediction model may help refine assessments of the thrombo-embolic risk with intermediate CHADS-2 risk scores.

References

[1] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2014;129:399–410.
[2] Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449–57.
[3] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:1360–420.
[4] Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011;58:395–401.
[5] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
[6] Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, et al. A risk scores for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290:1049–56.
[7] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010;137:263–72.
[8] Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886–91.
[9] Conway DS, Buggins P, Hughes E, Lip GY. Predictive values of indices of inflammation and hypercoaguability on success of cardioversion in persistent atrial fibrillation. Am J Cardiol 2004;94:508–10.
[10] Neuman RB, Bloom HL, Shukrullah I, Darrow LA, Kleinbaum D, Jones DP, et al. Oxidative stress markers are associated with persistent atrial fibrillation. Clin Chem 2007;53:1652–7.
[11] Dudley Jr SC, Hoch NE, McCann LA, Honeycutt C, Diamandopoulos L, Fukai T, et al. Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: role of the NADPH and xanthine oxidases. Circulation 2005;112:1266–73.
[12] Cai H, Li Z, Goette A, Mera F, Honeycutt C, Feterik K, et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation: potential mechanisms for atrial thrombosis and stroke. Circulation 2002;106:2854–8.
[13] Cornelli U, Terranova R, Luca S, Cornelli M, Alberti A. Bioavailability and antioxidant activity of some food supplements in men and women using the DROM tests as a marker of oxidative stress. J Nutr 2001;131:3208–11.
[14] Roberts LJ, Milne GL. Isoprostanes. J Lipid Res 2009;50:S219–23.
[15] Crandall MA, Horne BD, Day JD, Anderson JL, Muhlestein JB, Crandall BG, et al. Atrial fibrillation and CHADS-2 risk factors are associated with highly sensitive C-reactive protein incrementally and independently. Pacing Clin Electrophysiol 2009;32:648–52.
[16] Marott SC, Nordestgaard BG, Zacho J, Friberg J, Jensen GB, Tybjaerg-Hansen A, et al. Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population. J Am Coll Cardiol 2010;56:789–95.
[17] Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108:3006–10.
[18] Lip GY, Patel JV, Hughes E, Hart RG. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with non valvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. Stroke 2007;38:1229–37.
[19] Roldán V, Marín F, Díaz J, Gallego P, Jover E, Romera M, et al. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. J Thromb Haemost 2012;10:1500–7.
[20] Hermida J, Lopez FL, Montes R, Matsushita K, Astor BC, Alonso A. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol 2012;109:95–9.
[21] Conway DS, Buggins P, Hughes E, Lip GY. Relationship of interleukin-6 and C reactive protein to the prothrombotic state in chronic atrial fibrillation. J Am Coll Cardiol 2004;43:2075–82.
[22] Negi S, Sovari AA, Dudley Jr SC. Atrial fibrillation: the emerging role of inflammation and oxidative stress. Cardiovasc Hematol Disord Drug Targets 2010;10:262–8.
[23] Jeong EM, Liu M, Sturdy M, Gao G, Varghese ST, Sovari AA, et al. Metabolic stress, reactive oxygen species, and arrhythmia. J Mol Cell Cardiol 2012;52:454–63.
[24] Korantzopoulos P, Kolettis TM, Galaris D, Goudevenos JA. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. Int J Cardiol 2007;115:135–43.
[25] Guazzi M, Arena R. Endothelial dysfunction and pathophysiological correlates in atrial fibrillation. Heart 2009;95:102–6.
[26] Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:68–74.
[27] Jaulmes A, Sansilvestri-Morel P, Rolland-Valognes G, Bernhardt F, Gaertner R, Lockhart BP, et al. Nox4 mediates the expression of plasminogen activator inhibitor-1 via p38 MAPK pathway in cultured human endothelial cells. Thromb Res 2009;124:439–46.