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High Sensitivity C-Reactive Protein and Risk of Stroke in Atrial Fibrillation (From the Reasons for Geographic and Racial Differences in Stroke Study [REGARDS])

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Abstract

The relationship between inflammation and prothrombotic state in atrial fibrillation (AF) is well recognized. This suggests a potential role for high sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, in improving prediction of stroke in participants with AF. Cox proportional hazard analysis was used to examine the risk of stroke in 25,841 participants (40% black, 55% women) with and without AF who were enrolled in the REGARDS study between 2003 and 2007. Baseline AF (n=2,132) was ascertained by electrocardiogram and self-reported history of previous physician diagnosis. Stroke events were identified and adjudicated during 8.3 years of follow up. A total of 655 incident strokes occurred during follow up. In a model adjusted for socio-demographics, traditional stroke risk factors, and use of aspirin and warfarin, higher levels of hs-CRP were associated with increased overall stroke risk (HR (95% CI): 1.30 (1.10–1.54) and 1.06 (1.01–1.12) for hs-CRP > 3 mg/L and per 1-standard deviation (1-SD) increase,

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respectively. Higher levels of hs-CRP continued to be associated with incident stroke in participants without AF (HR (95%CI):1.31(1.09–1.57) and 1.06 (1.01–1.12) for hs-CRP> 3 mg/L and per 1-SD increase respectively) but not in those with AF (HR (95%CI): 1.22(0.78–1.91), and 1.01(0.82–1.23), for hs-CRP> 3 mg/L and per 1-SD increase respectively). In conclusion, although hs-CRP was significantly associated with stroke risk in this population, it seems to be limited to those without AF. These findings suggest a limited value of hs-CRP in improving stroke risk stratification in persons with AF.

Keywords

Atrial fibrillation; Stroke; hs-CRP; Inflammation

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice,¹ and it is an established risk factor for stroke, myocardial infarction and death.^{2–4} Previous studies have demonstrated increased risk of thrombogenesis in patients with AF.⁵ This thrombogenic tendency is believed to be related to abnormal changes in inflammatory biomarkers like C-reactive protein (CRP).⁶ High sensitivity CRP (hs-CRP), an acute phase reactant and an indicator of systemic inflammation, has been shown to be associated with atherothrombotic disease in patients with acute myocardial infarction and ischemia.^{7,8} Whether CRP predicts stroke differently in AF versus non-AF is not well established. This was only examined in few studies in which stroke was not the primary outcome or the focus was not on AF versus no AF or in populations that lack ethnic diversity or representation of both sexes.^{9–14} Therefore, we sought to examine and compare the relationship between baseline hs-CRP level and incident stroke events in participants with and without AF in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study.

Methods

The goals and design of the REGARDS study were published elsewhere.¹⁵ Briefly, the study was designed to investigate the causes of regional and racial disparities in stroke mortality, oversampling blacks and residents of the southeastern stroke belt region (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Individuals were recruited from a commercially available list of residents using a combination of postal and telephone contact with a 49% cooperation rate. Using a computer-assisted telephone interview, trained interviewers obtained demographic information and a cardiovascular medical history. Consent was obtained initially on the telephone and subsequently in writing during an in-person evaluation. In-home brief physical examinations were conducted 3 to 4 weeks after the telephone interview. Participants are followed every 6 months by telephone for possible stroke outcomes. Of the 30,239 REGARDS participants enrolled between 2003 and October 2007, we excluded 56 with anomalies associated with the informed consent process, 1,680 with prevalent stroke, 702 with missing AF data and 1,872 with no hs-CRP level recorded, resulting in 25,841 (85.6%) participants for analysis. The study was approved by the Institutional Review Boards of all participating universities.

Information on AF ascertainment was previously published¹⁶. AF was diagnosed based on baseline electrocardiogram (ECG) and self-reported history of a previous physician diagnosis. Self-reported previous physician diagnosis of AF was defined as a positive response to the question, “Has a physician or a health professional ever told you that you had AF?”

Details on stroke events identification and adjudication have been previously published.¹⁷ In summary, report of a possible stroke and/or transient ischemic attack or a positive response to the stroke symptoms on the Questionnaire for Verifying Stroke-Free Status¹⁸, resulting in hospitalization generated a request for retrieval of medical records that were centrally adjudicated by a panel of stroke expert physicians. Stroke events were defined according to the following World Health Organization definition as “rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”.¹⁹ Events not meeting the World Health Organization definition but characterized by symptoms lasting less than 24 h with neuroimaging consistent with acute ischemia or hemorrhage were classified as clinical strokes. This analysis included World Health Organization defined and clinical ischemic stroke cases through 2011.

Standardized physical measures including height, weight and blood pressure were collected at the in-home physical examination. Demographics (age, sex, and race) were defined by self-report. Stroke risk factors were selected based on the components of the CHADS2 Risk Score.²⁰ Congestive heart failure was defined as self-report of both orthopnea, defined as answering positively to “Do you ever have to sleep on 2 pillows to help you breathe?” and paroxysmal nocturnal dyspnea, defined as answering positively to “Do you ever wake at night because you are having trouble breathing?” Hypertension was defined as at least 1 of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or a self-report of currently taking medication to control blood pressure. Diabetes mellitus was defined as at least 1 of the following: fasting blood glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, or a self-report of currently taking an oral hypoglycemic agent or insulin. Current smoking and previous cardiovascular disease (defined by self-report (myocardial infarction or heart attack, coronary artery bypass surgery, coronary angioplasty, or stenting) or by ECG evidence of a previous myocardial infarction) were included. Use of antihypertensive, lipid lowering, and glucose lowering medications, current warfarin treatment and consistent aspirin use were defined using an inventory of current medications that was conducted during the in-home visits.

Frequency distributions of all variables were first inspected to identify anomalies and outliers possibly caused by measurement artifacts. Continuous data were described by their mean and SD and categorical data as proportions (percentage). Cox proportional hazards analysis was used to examine the hazard ratios (HR) and 95% confidence interval (CI) for the association of stroke with hs-CRP > 3 mg/l compared to ≤ 3 and per 1 standard deviation (1-SD) increase in the entire population, participants with AF and participants without AF, separately. Models were first adjusted for baseline socio-demographics (age, sex, race, education and income) (Model 1); and then further adjusted for congestive heart failure, hypertension, diabetes warfarin and/or aspirin use (Model 2). Stroke free survival curves in

participants with and without AF population with hs-CRP > vs. < than 3mg/L were also created. All analyses were performed with SAS version 9.3 [SAS Institute Inc., Cary, North Carolina].

Results

A total of 25,841 participants (40% black, 55% women, age > 45 years) were included in this analysis. AF was detected in 2,132 of participants at baseline. The median hs-CRP level at baseline was higher in the AF group (2.6 mg/L (IQR: 1.09–6.03) compared to hs-CRP in the group without AF (2.1 mg/L (IQR: 0.93–4.89); $p < 0.01$).

Table 1 shows the baseline characteristics of the participants stratified by AF status and hs-CRP level > or < than 3mg/L. Participants with hs-CRP level > 3mg/L regardless of AF status were more likely to be women, black and have more comorbid condition like hypertension, diabetes, CHF, obesity and more likely to be on aspirin and warfarin therapy.

During 8.3 years of follow up, 655 incident strokes occurred of which 99 occurred in the AF group and 556 in the group without AF. Among participants with AF, baseline hs-CRP (< vs < than 3mg/L) did not influence stroke risk ($p=0.67$). However, higher hs-CRP was associated with increased stroke risk in population without AF ($p=0.001$) (Figure 1).

Table 2 shows the risk of stroke associated with higher levels of hs-CRP (>3mg/l and per 1-SD increase) in the overall population and in those with and without AF separately. As shown, overall higher levels of hs-CRP were associated with increased risk of stroke in both model 1 (sociodemographic model) and 2 (full model). However, higher levels of hs-CRP were associated with incident stroke in participants with and without AF in model 1 but only in the AF group after adjusting for variables in model 2. This suggests that the association between hs-CRP and stroke in AF was largely explained by covariates added to model 2. Similar results were obtained when participants with history of prior stroke at baseline were not excluded and adjusted for prior stroke in the model (data not shown).

Discussion

In this analysis from the REGARDS study, we found that higher levels of hs-CRP are associated with stroke in those without AF but not in those with AF. This suggests a limited value of hs-CRP in improving stroke risk stratification in participants with AF.

The temporal relationship between AF and inflammation, casual vs secondary, remains unclear, but there is considerable evidence in the literature on the association between inflammation and AF.²¹ Cytokines, especially IL-6, illicit the expression of hs-CRP. As a dynamic marker of inflammation, hs-CRP provides a window to the inflammatory state of the individual which dramatically increases in response to tissue damage.²² We have shown in this analysis that the group of participants with prevalent AF has higher levels of hs-CRP compared to the non-AF group which is consistent with previous studies in the literature.

Chronic elevation of hs-CRP has been shown to be predictive of increased stroke risk.^{10–14} A study from the Third National Health and Nutrition Examination Survey (NHANES)

examined the association between CRP concentrations and self-reported past history of stroke among 8850 US men and women aged 40 years. The results revealed that higher concentration of CRP is associated with greater risk of stroke.²³ In the Framingham Study, elevated plasma CRP levels were shown to be significantly predictive of the risk of future ischemic stroke and TIA in the elderly independent of other cardiovascular risk factors.¹³ In the current analysis, we showed that baseline hs-CRP is associated with increased risk of stroke in a well-represented biracial US population without AF and the relationship remained significant after adjustment for traditional stroke risk factors. The findings of this study support previous studies suggesting that elevated hs-CRP level may be a marker of increased risk of stroke but not necessarily stronger in participants with AF despite the fact of having higher levels of hs-CRP.

It has been previously shown that patients with cardio-embolic stroke compared to other subtypes had significantly higher median levels of multiple inflammatory markers like TNF-alpha, IL-6 and IL-1beta²⁴. In fact, once an ischemic event transpires, the expression of inflammatory molecules and activation of quiescent inflammatory cells leads to inflammatory state for several months after initial insult.^{25,26} In a study investigating the relationship between hs-CRP and stroke risk in 880 participants, baseline hs-CRP levels were shown to be predictive of mortality and vascular death in AF, but not stroke.²⁷ Indeed, the timing of inflammation may post date the ischemic insult. Furthermore, although AF itself may lead to an inflammatory state²¹, once an inflammatory state is achieved, the year to year within person variation of hs-CRP levels are similar to those in cholesterol and systolic blood pressure and the risk of future disease can be underestimated using a single measure at baseline.²⁸ Therefore, it is plausible that participants that suffer a stroke in the setting of known AF are previously in chronic inflammatory state which makes detection of association between inflammation and stroke difficult. In addition, most individuals with AF are more likely to have various comorbidities and risk factors like hypertension, obesity, and diabetes which could further enhance the baseline inflammatory state.¹⁴ That is to say, AF represents the culmination of several conditions that are pro-inflammatory. Therefore, it is expected that inflammation will not predict stroke in AF, as they have already suffered the consequences of higher levels of inflammation. The opposite could be true for those without AF, which may explain why hs-CRP was associated with stroke in those without AF but not those with AF.

We acknowledge certain limitations of our study. Our conclusion that the association between hs-CRP with stroke is limited to those without AF is based on qualitative comparison between the hazard ratios and the consistent non-significant p-value associated with hs-CRP in the AF group regardless of how hs-CRP is used in the model. However, the number of participants in the AF group was less than that in the non-AF group which raises the possibility that low statistical power may explain the lack of association in the AF group. Nevertheless, the high event rate (stroke cases) in the AF group should lessen this concern to some extent. AF in our study was ascertained by two methods (self-report of a previous physician diagnosis and study ECG), and self-report of a previous physician diagnosis of AF could be subject to recall and ascertainment bias. However, we have previously shown that self-report of a previous physician diagnosis of AF has similar stroke predictive value as ECG in the REGARDS study.¹⁶ Finally, participants who are unaware of AF status on

enrollment but informed later may have been started on treatment including anticoagulation which we could not consider in the models.

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Figure 1. Unadjusted Kaplan Meier survival curves for event free survival in participants without (1-A) and with (1-B) atrial fibrillation stratified by high sensitivity C-reactive protein levels (vs. > 3mg/l)

Table 1
Baseline characteristic of participants by atrial fibrillation status and high sensitivity C-reactive protein levels

Characteristics*	No Atrial Fibrillation			Atrial Fibrillation		
	HS-CRP 3.0 mg/l	HS-CRP 3.0 mg/l	p-value [†]	HS-CRP 3.0 mg/l	HS-CRP 3.0 mg/l	p-value [†]
Participants (n)	14333	9376	1165	967		N/A
Age (year)	64.5±9.5	64.0±9.1	<0.001	66.4±9.5		<0.001
Men	51.5%	35.4%	<0.001	39.0%		<0.001
Black	34.8%	49.0%	<0.001	43.0%		<0.001
Hypertension	51.4%	64.3%	<0.001	72.8%		<0.001
Diabetes Mellitus	16.4%	24.2%	0.0182	27.8%		0.002
Dyslipidemia	56.7%	58.3%	0.012	64.4%		0.76
Body mass index (kg/m ²)	27.8±5.1	31.5±6.8	<0.001	31.2 ±7.1		<0.001
Smoker (Ever)	52.0%	51.7%	<0.001	62.6%		<0.001
Heart failure	2.8%	5.5%	<0.001	16.4%		<0.001
Coronary heart disease	9.9%	10.8%	<0.001	24.7%		0.82
Aspirin	42.8%	39.2%	<0.001	46.3%		0.005
Warfarin	1.1%	1.8%	<0.001	21.0%		0.98

* Values are expressed as % and mean ± SD unless mentioned otherwise.

[†] p-value calculated using t-test for continuous variables and chi² for categorical variables.

Table 2

Risk of stroke associated with high levels of high sensitivity C-reactive protein stratified by baseline atrial fibrillation status

	Hs-CRP mg/l	Participants (n)	Incidence rate Per 1000 pt-yr	Model 1* Hazard ratio (95% CI)	Model 2† Hazard ratio (95% CI)
Overall	3.0	15,498	4.7	Reference	Reference
	> 3.0	10,343	6.1	1.38 (1.18–1.65)	1.30 (1.10–1.54)
	Per 1-SD increase‡	25,841	5.3	1.07 (1.02–1.13)	1.06 (1.01–1.12)
No Atrial Fibrillation	3.0	14,333	4.3	Reference	Reference
	> 3.0	9,376	5.7	1.39 (1.16–1.67)	1.31 (1.09–1.57)
	Per 1-SD increase‡	23,709	4.8	1.08 (1.02–1.13)	1.07 (1.01–1.13)
Atrial Fibrillation	3.0	1,165	9.8	Reference	Reference
	> 3.0	967	10.7	1.31 (1.16–2.04)	1.22 (0.78–1.91)
	Per 1-SD increase‡	2,132	10.2	1.03 (0.82–1.19)	1.01 (0.82–1.23)

Model 1, adjusted for age, sex, race and socioeconomic status (income and education level)

†Model 2, adjusted for variables in Model 1 plus hypertension, diabetes mellitus, congestive heart failure and warfarin/aspirin use

‡SD= standard deviation of high sensitivity C-reactive protein in the overall REAGRDS; 8.61 mg/l