

# Inflammation as a Risk Factor for Atrial Fibrillation

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**Background**—The presence of systemic inflammation determined by elevations in C-reactive protein (CRP) has been associated with persistence of atrial fibrillation (AF). The relationship between CRP and prediction of AF has not been studied in a large population-based cohort.

**Methods and Results**—CRP measurement and cardiovascular assessment were performed at baseline in 5806 subjects enrolled in the Cardiovascular Health Study. Patients were followed up for a mean of  $6.9 \pm 1.6$  (median 7.8) years. AF was identified by self-reported history and ECGs at baseline and by ECGs and hospital discharge diagnoses at follow-up. Univariate and multivariate analyses were used to assess CRP as a predictor of baseline and future development of AF. At baseline, 315 subjects (5%) had AF. Compared with subjects in the first CRP quartile ( $<0.97$  mg/L), subjects in the fourth quartile ( $>3.41$  mg/L) had more AF (7.4% versus 3.7%, adjusted OR 1.8, 95% CI 1.2 to 2.5;  $P=0.002$ ). Of 5491 subjects without AF at baseline, 897 (16%) developed AF during follow-up. Baseline CRP predicted higher risk for developing future AF (fourth versus first quartile adjusted hazard ratio 1.31, 95% CI 1.08 to 1.58;  $P=0.005$ ). When treated as a continuous variable, elevated CRP predicted increased risk for developing future AF (adjusted hazard ratio for 1-SD increase, 1.24; 95% CI 1.11 to 1.40;  $P<0.001$ ).

**Conclusions**—CRP is not only associated with the presence of AF but may also predict patients at increased risk for future development of AF. (*Circulation*. 2003;108:3006-3010.)

**Key Words:** atrial flutter ■ fibrillation ■ inflammation ■ arrhythmia

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, affecting 2.3 million people in the United States.<sup>1</sup> A major cause of stroke, AF is also associated with a 2-fold increase in mortality.<sup>2,3</sup> Although a number of risk factors have been associated with AF, acute or chronic hemodynamic, metabolic, or inflammatory stressors may lead to structural remodeling of the atria that may promote progression and persistence of AF.

The concept that inflammation contributes to at least some types of AF is supported by the frequent occurrence (25% to 40%) of AF after cardiac surgery,<sup>4</sup> genetic studies,<sup>5</sup> and the association of AF with pericarditis.<sup>6</sup> The temporal course of AF occurring after cardiac surgery closely follows the activation of the complement system and release of proinflammatory cytokines.<sup>4,7</sup>

We hypothesized that nonpostoperative forms of AF may also be related to inflammation. Supporting this hypothesis is the observation of inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF

refractory to antiarrhythmic drug therapy.<sup>8</sup> Also, in a case-control study of patients with AF, we found that C-reactive protein (CRP) levels were higher in patients with AF than in a control group of patients in normal sinus rhythm.<sup>9</sup> Selection bias may have limited this case-control study, and the temporal relation between elevated CRP and AF could not be assessed.

Population-based studies have not evaluated the relation between inflammation and AF. We used data from the Cardiovascular Health Study (CHS) to test the hypothesis that elevated levels of CRP predict subjects at increased risk for AF.

## Methods

The CHS<sup>10</sup> is a large, population-based study of cardiovascular disease in the elderly sponsored by the National Heart, Lung, and Blood Institute. We performed 2 separate studies to evaluate the relation between CRP and AF. In the first study, we performed a cross-sectional analysis to determine the association between CRP and baseline AF. In the second study, we performed a longitudinal analysis to evaluate the relation between baseline CRP and development of new cases of AF.

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## Study Population

Between 1989 and 1990, 5201 noninstitutionalized men and women aged 65 years or older were enrolled using random samples from Medicare eligibility lists from 4 communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pa. Because 94% were white, a second cohort of 687 black participants was enrolled between 1992 and 1993. Of the 5888 total subjects, 5806 with available baseline CRP measurements composed the cohort of the current study. All participants provided written informed consent, and the institutional review boards at all participating sites, including the Coordinating Center in Seattle, Wash, approved the study protocol.

Participants underwent a comprehensive examination at baseline, which included a thorough medical history, physical examination, laboratory testing, a 12-lead ECG, and assessment of cardiovascular disease status. Details of the study design, quality-control procedures, laboratory methods, and definitions of coronary heart disease (CHD), cerebrovascular disease, hypertension, and diabetes mellitus have been reported elsewhere.<sup>10,11</sup> Echocardiograms were obtained for evaluation of left ventricular ejection fraction.<sup>12</sup>

Participants were followed up every 6 months through alternating telephone interviews and annual clinic visits. At each annual clinic evaluation, participants had a 12-lead ECG and were asked about hospital admissions. Diagnoses and hospital records were obtained for all hospital admissions, and the events committees adjudicated cardiovascular events. Discharge diagnoses and cardiovascular events were tracked and recorded in the CHS events database.

## Defining Cases of AF

Cases of AF were identified by 3 validated methods: (1) self-report, (2) ECG, and (3) hospital discharge diagnosis. A study of AF prevalence in CHS found that in subjects with AF, medication pattern indicated that self-reported AF was reliable.<sup>13</sup> The reported accuracy of the hospital discharge diagnosis of AF in CHS (International Classification of Diseases, 9th Revision [ICD 9] codes 427.3, 427.31, or 427.32) is 98.3%.<sup>14</sup> ECGs from annual clinic visits, and not ECGs from hospitalizations, were reviewed at the CHS Electrocardiographic Reading Center.<sup>15</sup>

For the cross-sectional study, cases of AF were defined as AF by self-report and AF by ECG. All cases of baseline AF were excluded from the longitudinal study. New cases of AF in the longitudinal study were defined as AF by ECG and AF by hospital discharge diagnosis.

## CRP Analysis

Baseline blood samples were obtained early in the day after an overnight fast. Plasma and serum samples were collected in aliquots, frozen at  $-70^{\circ}\text{C}$ , and shipped to the CHS Core Laboratory, where they were analyzed. Personnel blinded to clinical data performed CRP measurements. An ultrasensitive ELISA developed at the CHS Core Laboratory was used to measure CRP.<sup>16</sup> The interassay coefficient of variation is 5.5%.<sup>17</sup>

## Statistical Methods

CRP was assessed for distributional properties. Because the distribution of CRP was highly skewed, logarithmic transformation of CRP was used for the logistic regression and time-to-event analyses. CRP levels were reported as untransformed values. Risk factors for AF considered in the multivariate analyses included age, gender, race, body mass index (kilogram per meter squared), left ventricular dysfunction, systolic and diastolic blood pressures, history of hypertension, CHD, diabetes mellitus, cerebrovascular disease, and congestive heart failure.

For the cross-sectional study, baseline characteristics were analyzed by  $\chi^2$  or Kruskal-Wallis tests according to quartiles of CRP. The association between CRP and AF at baseline was estimated with multivariate logistic regression models. Odds ratios (ORs) for AF were calculated in 2 ways: by modeling CRP as a continuous variable and by categorizing CRP into quartiles and comparing each quartile to the first quartile of CRP. Models were developed by a

directed, forward stepwise selection technique and confirmed with bootstrap random resampling. The association between CRP and development of future AF was estimated with multivariate Cox proportional-hazards regression models and the Kaplan-Meier method. Event time was defined as the date of first follow-up examination ECG or first hospitalization in which AF occurred. Hazard ratios (HRs) for AF were calculated in 2 ways: by modeling CRP as a continuous variable and by categorizing CRP into quartiles and comparing each quartile to the first quartile of CRP. Models were created with a directed, forward stepwise selection technique. To assess whether the effect of CRP was independent of the method used to identify new cases of AF, we developed separate models for each method. The association of CRP and risk of developing future AF was also determined in prespecified subsets: subjects with and without CHD, diabetes, or hypertension; smoking history; and male gender.

All statistical testing was 2-sided. Results were considered statistically significant at a level of  $P < 0.05$ . All analyses were performed with SAS statistical software (SAS Institute).

## Results

### Cross-Sectional Study of CRP and Baseline AF

Of 5888 subjects enrolled in CHS, 82 without CRP measurement were excluded. Of 5806 subjects included in the cross-sectional study, 315 (5%) had AF at baseline. Mean age was  $73 \pm 5$  years; 2465 (42%) were men; and 887 (15%) were black. Table 1 shows baseline characteristics according to quartiles of CRP. Mean  $\pm$  SD and median CRP values were  $3.64 \pm 6.31$  and 1.92 mg/L, respectively (interquartile range 0.97 and 3.41 mg/L). Subjects in higher quartiles of CRP had a more adverse risk profile. CRP levels were higher among subjects with AF (median 2.41 mg/L, interquartile range 1.29 to 5.02 versus 1.89 mg/L, interquartile range 0.95 to 3.37;  $P < 0.001$ ).

Table 2 shows unadjusted and adjusted risk for AF according to quartiles of CRP. The risk for AF was progressively higher with increasing CRP quartiles. After adjustment for multiple variables potentially associated with AF, CRP remained an independent predictor of baseline AF. Unadjusted and adjusted ORs for AF were also estimated with CRP treated as a continuous variable (unadjusted OR for 1-SD increase in CRP 1.48, 95% CI 1.22 to 1.80,  $P < 0.001$ ; adjusted OR 1.31, 95% CI 1.07 to 1.60,  $P < 0.001$ ).

### Longitudinal Study of CRP and Prediction of Future AF

After 315 subjects with baseline AF were excluded, 5491 were included in the longitudinal study of CRP and prediction of future AF. Of 897 subjects who developed AF during follow-up, 64 (1%) had AF by ECG, 675 (12%) had AF by hospital discharge diagnosis, and 158 (3%) had AF by both methods. Subjects were followed up for a mean of  $6.9 \pm 1.6$  (median 7.8) years.

Table 3 shows the unadjusted and adjusted risk for developing future AF according to quartiles of CRP. Higher CRP quartiles were associated with a higher risk of developing AF during follow-up. After adjustment for multiple factors potentially associated with AF, the highest quartile of CRP remained an independent predictor of future development of AF.

When analyzed as a continuous variable, increasing CRP levels predicted a 33% greater likelihood of developing AF (unadjusted HR for a 1-SD increase in CRP 1.33, 95% CI

**TABLE 1. Baseline Characteristics According to CRP Quartiles**

	Variable CRP, mg/L				<i>P</i>
	Q1 (<0.97) (n=1446)	Q2 (0.97–1.92) (n=1454)	Q3 (1.92–3.41) (n=1447)	Q4 (>3.41) (n=1459)	
Age, y	73.2±5.8	72.7±5.4	72.7±5.5	72.6±5.5	0.05
Male, %	55	54	59	62	<0.001
White, %	88	87	84	77	<0.001
Diabetes, %	20	26	32	40	<0.001
Hypertension, %	49	55	63	67	<0.001
Smoker, %	50	53	54	58	<0.001
CHD, %	23	26	30	33	<0.001
LV dysfunction moderate/severe, %	7	8	10	12	<0.001
Congestive heart failure, %	3	4	4	8	<0.001
Body mass index, kg/m <sup>2</sup>	24.7±3.8	26.1±3.9	27.4±4.6	28.5±5.5	<0.001
Systolic blood pressure, mm Hg	134.1±21.6	136.3±21.8	138.1±21.9	137.4±21.5	<0.001
Diastolic blood pressure, mm Hg	70.0±11.2	71.1±11.2	70.8±11.5	70.9±11.6	0.11

Q indicates quartile; LV, left ventricular. Continuous variables are presented as mean±SD; categorical variables are presented as percentages.

1.18 to 1.49,  $P<0.001$ ). Multivariate Cox regression analysis treating CRP as a continuous variable (Table 4) confirmed the association between CRP and risk of future development of AF even after adjustment for CHD, left ventricular dysfunction, older age, male gender, systolic or diastolic blood pressure, cerebrovascular disease, body mass index, congestive heart failure, diabetes, and hypertension. There were no interactions between CRP and these variables.

To determine whether prediction of new cases of AF by elevated levels of CRP was independent of the method used to identify cases of AF, 2 other Cox regression univariate models were developed, one for cases of AF identified by ECG and the other for cases of AF identified by hospital discharge diagnosis. Elevated CRP levels predicted subjects at increased risk for developing future AF whether identified by ECG (HR for 1-SD increase in CRP 1.26, 95% CI 1.03 to 1.53,  $P=0.025$ ) or by hospital discharge diagnosis (HR for 1-SD increase in CRP 1.37, 95% CI 1.18 to 1.57,  $P<0.001$ ).

Figure 1 shows the unadjusted risk of developing future AF among prespecified subsets of patients. CRP predicted patients at increased risk for developing AF across all subsets tested, including subjects with and without CHD.

Figure 2 shows Kaplan-Meier AF-free survival curves comparing patients above and below the median CRP level of

1.92 mg/L. The curves separate steadily throughout the entire follow-up period, without a higher number of early versus late cases of AF. The rate of new cases of AF was 25 new cases per 1000 population per year.

## Discussion

In this analysis of a population-based study of cardiovascular disease in the elderly, CRP was independently associated with baseline AF and with the future development of AF over a mean follow-up of 6.9 years. In both the cross-sectional and the longitudinal studies, CRP remained a significant predictor of AF even after adjustment for multiple risk factors for AF, including hypertension and CHD.

The strength of the association between CRP and future onset of AF was similar to the relation found with other traditional risk factors for AF (Table 4).<sup>2,3,18</sup> For example, the adjusted HR for a 1-SD increase in systolic blood pressure of 1.14 ( $P<0.002$ ) is comparable to the adjusted HR for a 1-SD increase in CRP of 1.24 ( $P<0.001$ ).

The relation between elevated baseline CRP levels and future development of AF was not only present across all prespecified subgroups but was also independent of the method used to identify new cases of AF. Furthermore, the concentration-response relation of CRP levels and risk for AF

**TABLE 2. Cross-Sectional Study: Baseline AF According to CRP Quartiles**

CRP Quartiles, mg/L	AF Cases/No. at Risk	Unadjusted OR (95% CI)	<i>P</i>	Adjusted* OR (95% CI)	<i>P</i>
<0.97	54/1446	1.00	...	1.00	...
0.97 to 1.92	72/1454	1.34 (0.94–1.93)	0.110	1.33 (0.92–1.92)	0.130
1.93 to 3.41	81/1447	1.53 (1.08–2.18)	0.020	1.45 (1.02–2.07)	0.040
>3.41	108/1459	2.07 (1.48–2.89)	<0.001	1.75 (1.24–2.46)	0.002

\*Variables considered in the multivariate analyses included age, gender, race, systolic and diastolic blood pressures, left ventricular dysfunction, body mass index, CRP, history of CHD, congestive heart failure, diabetes mellitus, hypertension, cerebrovascular disease, and smoking.

**TABLE 3. Longitudinal Study: AF According to CRP Quartiles**

Quartiles of CRP, mg/L	Unadjusted HR (95% CI)	P	Adjusted* HR (95% CI)	P
<0.97	1.00	...	1.00	...
0.97 to 1.92	0.94 (0.78–1.14)	0.54	0.90 (0.74–1.09)	0.290
1.93 to 3.41	1.13 (0.94–1.36)	0.200	1.09 (0.90–1.32)	0.370
>3.41	1.42 (1.18–1.70)	<0.001	1.31 (1.08–1.58)	0.005

\*Variables considered in the multivariate analyses included age, gender, race, systolic and diastolic blood pressures, left ventricular dysfunction, body mass index, CRP, CHD, congestive heart failure, diabetes mellitus, hypertension, cerebrovascular disease, and smoking.

demonstrated both in the cross-sectional study and the longitudinal study (Tables 2 and 3) strengthens the association between CRP and AF.

The absence of an early cluster of cases of AF in Figure 2 suggests that cases of clinically overt AF at baseline were indeed excluded from the longitudinal study. The rate of future onset of AF cases of 25 per 1000 population per year in the present study (mean age 73±5 years) is consistent with annual incidence rates reported in the literature, which range from 2 or 3 new cases for patients between the ages of 55 and 64 years to 35 new cases per 1000 population per year for patients between the ages of 85 and 94 years.<sup>7</sup> Nevertheless, the definition of new cases of AF in the present study could potentially exclude the detection of cases of paroxysmal AF that might not have resulted in persistent AF detected by ECG or by hospital diagnosis. However, CRP and the presence of systemic inflammation may be more predictive of persistent AF, as might be better detected in the present study, rather than paroxysmal AF.<sup>9</sup>

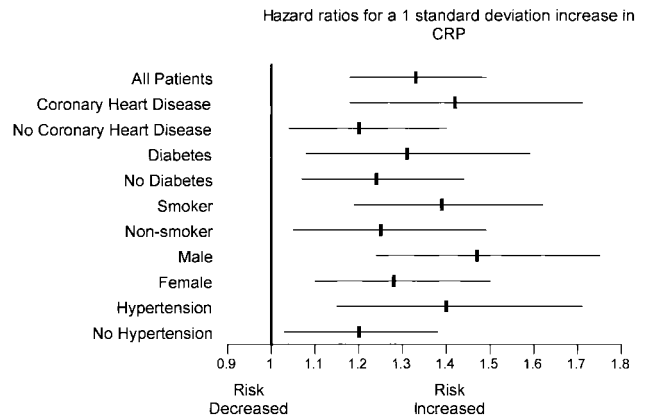
These results confirm the association of CRP with AF reported in a case-control study from our group showing that

**TABLE 4. Longitudinal Study: Multivariate\* Cox Regression Analysis for Risk of Developing Future Onset of AF**

Risk Factor	χ <sup>2</sup>	HR	95% CI	P
Age (per 1-SD increase)	84	1.36	1.27–1.45	<0.001
Male gender	59	1.71	1.49–1.96	<0.001
CHD	21	1.40	1.21–1.62	<0.001
Congestive heart failure	22	1.88	1.45–2.45	<0.001
CRP (per 1-SD increase)	13	1.24	1.11–1.40	<0.001
Cerebrovascular disease	10	1.42	1.14–1.77	0.001
Left ventricular dysfunction	10	1.40	1.13–1.72	0.001
Systolic blood pressure (per 1-SD increase)	9	1.14	1.05–1.25	0.002
Race†	7	1.55	1.13–2.12	0.006
Hypertension	8	1.28	1.08–1.51	0.005
Diastolic blood pressure (per 1-SD increase)	5	0.92	0.85–0.99	0.028
Diabetes	5	1.18	1.02–1.36	0.022

\*Variables considered in the multivariate analyses included age, gender, race, systolic and diastolic blood pressures, left ventricular dysfunction, body mass index, CRP, CHD, congestive heart failure, diabetes mellitus, hypertension, cerebrovascular disease, and smoking.

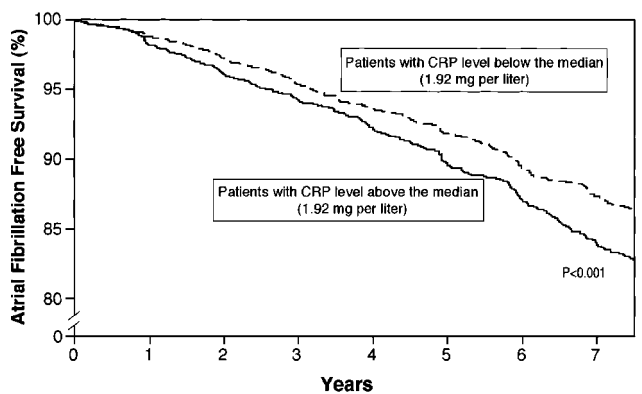
†Other than white.



**Figure 1.** CRP and risk of developing future onset of AF among prespecified subgroups. Unadjusted HR for 1-SD increase in CRP were derived by Cox regression analysis. CRP predicted patients at increased risk for future development of AF across all subgroups tested, including patients with and without CHD.

CRP was >2-fold higher among patients with AF than among controls.<sup>9</sup> Higher CRP levels were observed among patients with persistent compared with paroxysmal AF and in patients with AF compared with patients in sinus rhythm. These results are consistent with both the cross-sectional and longitudinal AF associations found in the present study.

It has become clear in recent years that important triggers initiating AF arise from focally discharging cells located most commonly at the pulmonary vein ostia.<sup>19</sup> These foci may lead to frequent atrial ectopy and paroxysms of AF. Whether initiation of AF activates direct inflammatory effects or whether the presence of a preexisting systemic inflammatory state promotes further persistence of AF remains unclear. The high rate activity of AF may lead to myocyte calcium overload and in some cases to the initiation of apoptotic loss of atrial myocytes.<sup>20</sup> CRP has been shown to act as an opsonin and may participate in the clearance of apoptotic myocytes.<sup>21</sup> Myocyte loss is typically accompanied by replacement fibrosis. This low-level inflammatory response may thus be part of the structural remodeling process associated with increased persistence of AF.<sup>22,23</sup> Alternatively, the



**Figure 2.** AF-free survival for subjects below and above median CRP level. Event-free survival for patients below and above median CRP value of 1.92 mg/L was obtained by Kaplan-Meier method. Subjects above median CRP value of 1.92 mg/L had lower AF-free survival (log rank, P<0.001).

presence of a baseline elevated level of systemic inflammation may predispose patients with triggering atrial foci to development or persistence of AF, as might be detectable in the present study, years from the initial baseline measurement of CRP. This worsened progression of the arrhythmia in the presence of systemic inflammation may be analogous to that observed in other states in which elevated CRP is associated with worsened outcomes. An example would be acute coronary syndromes in which the presence of high CRP is associated with worsened mortality and left ventricular dysfunction,<sup>24</sup> potentially reflecting a propensity for ventricular remodeling.

The association of inflammation with AF may have potential therapeutic implications. Various therapeutic strategies have the potential to modify CRP levels, including statins.<sup>25</sup> However, the efficacy of these therapies in preventing persistence of AF among patients with elevated CRP is unknown. The effect of these therapies on the risk of developing AF could not be evaluated in the present study owing to the low number of subjects receiving these agents. At the time of enrollment in 1989 to 1990 and in 1992, fewer than 2.3% of subjects were taking statins.

### Study Limitations

As with other epidemiological studies, the ascertainment and classification of AF is a potential limitation of the present study, and AF may have occurred outside of the annual clinic visits or hospitalizations. The type of AF, whether symptomatic or asymptomatic (paroxysmal, persistent, or chronic), cannot be fully discriminated in this study. A cause-effect relationship cannot be firmly established. It is possible that uncorrected confounding might explain the prediction of new cases of AF by CRP. Our results, however, add to a growing body of evidence linking inflammation to the occurrence and persistence of AF.

### Conclusions

In this large, population-based study of cardiovascular disease in the elderly, CRP, a marker of systemic inflammation, was independently associated with the presence of AF at baseline. CRP also predicted patients at increased risk for developing future AF. Although a causal relationship cannot be established, these findings support a possible association of an inflammatory state and future development of AF.

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