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White Blood Cell Count and Risk of Incident Atrial Fibrillation (From the Framingham Heart Study)

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Abstract

Several studies have reported that inflammatory markers are associated with atrial fibrillation (AF). White blood cell (WBC) count is a widely available and broadly utilized marker of systemic inflammation. We sought to investigate the association between increased WBC count and incident AF, and whether this association is mediated by smoking, myocardial infarction and heart failure. We examined participants in the Framingham Heart Study Original Cohort. Cox proportional hazard regression analysis was used to examine the relation between WBC count and incident AF over 5-year follow-up period. We adjusted for standard AF risk factors, and smoking, previous myocardial infarction, as well as interim myocardial infarction and heart failure prior to incident AF. Our sample consisted of 936 participants, mean age was 76±6 years and 61% were women. Median WBC count was 6.4*10⁹/L (25th-75th percentile 5.6*10⁹/L- 7.8*10⁹/L). During a median follow-up of 5 years, 82 participants (9%) developed new-onset AF. After adjusting for standard risk factors for AF, increased WBC count was significantly associated with incident AF, with a hazard ratio per standard deviation (0.26*10⁹/L) increase of 2.22, (95% confidence interval, 1.10–4.48; *P*=0.03). We found no substantive differences adjusting for smoking, previous myocardial infarction, interim myocardial infarction and heart failure. In conclusion, in our community-based sample, increased WBC count was associated with incident AF during 5-years of follow-up. Our findings provide additional evidence for the relation between systemic inflammation and AF.

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Keywords

Atrial fibrillation; blood cells; inflammation; risk factors

The most widely available marker of systemic inflammation is white blood cell (WBC) count. To date, the relations between WBC count and atrial fibrillation (AF) have not been extensively explored. Increased WBC count during the perioperative period was predictive of post-operative AF,¹⁻⁴ and a small observational study observed that increased WBC count was associated with recurrence of AF post-pulmonary vein isolation.⁵ However, whether increased WBC count is associated with AF in the general population is unclear. We hypothesized that increased WBC count is related to incident AF in the community. We further postulated that the relation between WBC count and incident AF may be attenuated by adjustment for factors associated with inflammation that may serve as potential mediators of an association between WBC and AF, including body mass index, smoking, previous myocardial infarction, as well as interim myocardial infarction and heart failure prior to incident AF.

Methods

We studied participants from the Framingham Heart Study Original Cohort; participants were initially recruited in 1948.⁶ For the present analysis, we used data from 1401 participants attending the twentieth biennial examination cycle (1986–1990). Participants were excluded for the following reasons: prevalent AF (n=120); missing WBC count (n=315); and missing covariate data (body mass index [n=24], PR interval [n=3], hypertension treatment [n=2], and cardiac murmur [n=1]). Characteristics of included versus excluded participants attending the 20th examination cycle are reported in Supplementary Table 1. Participants were monitored until the first AF event with a maximum follow-up duration of five years. In secondary analyses follow-up duration was increased to ten years. The Boston University Medical Center Institutional Review Board approved the protocol of the Framingham Heart Study and all participants signed informed consent.

Body mass index was calculated as weight in kilograms divided by height in meters squared. Ascertainment of antihypertensive treatment was by self-report. Current smoking was defined as self-reported regular use of cigarettes in the year preceding examination. A clinically significant precordial murmur was diagnosed when a physician auscultated a systolic murmur at least grade 3 of 6 intensity, or any diastolic murmur. Subjects were diagnosed with heart failure based on standard major and minor clinical criteria.⁷

Non-fasting blood samples were obtained the morning of the Framingham Heart Study clinic visit and frozen at -80°C . Plasma WBC count was measured with Serono-Baker System 9000 Hematology Analyzer (Serono-Baker Diagnostics, Allentown, PA, USA). Normal range of WBC count using this analyzer was $3.8 - 12.4 \times 10^9/\text{L}$.

Atrial fibrillation was considered present if either atrial flutter or atrial fibrillation was present on an electrocardiogram, Holter monitor or outside clinical records. Records were obtained at Framingham Heart Study clinic visits, on outside clinician visits, or during hospital admissions, and a Framingham Study cardiologist reviewed all.

In our primary analysis we tested the hypothesis that higher WBC count is related to incident AF using Cox proportional hazards regression analysis. We examined robust variance estimators to account for relatedness among Framingham Heart Study participants. We examined the appropriateness of the proportionality assumption by including time dependent risk factors (i.e., interactions between risk factors and log(time)). The time

dependent risk factors were not statistically significant, supporting the assumption of proportionality of hazards. Since WBC count was positively skewed, WBC count was natural logarithmically-transformed ($\log_e$). We used one standard deviation of the $\log_e$ WBC count to quantify the effect size. We examined the association between WBC count and incident AF in age- and sex- adjusted models, and in multivariable models adjusted for established AF risk factors, as used in a previously published Framingham Heart Study AF risk score.⁸ Variables in the AF risk score include age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, and heart failure. In secondary analyses, we additionally adjusted for smoking, previous myocardial infarction, interim myocardial infarction, and interim heart failure. We performed additional models using the method of Fine and Gray to adjust the risk estimates for the competing risk of death.⁹ All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC), and R software, version 2.11.1 (R Foundation for Statistical Computing) and a two-tailed p-value of <0.05 was considered statistically significant.

Results

Our final sample consisted of 936 participants. The mean age was 76 ± 6 years and 61% were women. Myocardial infarction was present in 10% of participants, and 10% were current smokers. The median WBC count was $6.4 \times 10^9/L$ (25th - 75th percentile $5.6 \times 10^9/L$ - $7.8 \times 10^9/L$). Sample characteristics are displayed in Table 1. The standard deviation (SD) of the $\log_e$ WBC count was $0.26 \times 10^9/L$.

During a median follow-up of 5 years, 82 participants (9%) developed incident AF. After adjusting for standard risk factors for AF, $\log_e$ WBC count was significantly associated with incident AF, with a hazard ratio of 2.22 per SD increase; 95% confidence interval, 1.10–4.48; $p=0.03$; Table 2). In Figure 1 the cumulative incidence of AF by tertiles of the WBC count distribution is shown.

To test whether smoking, previous myocardial infarction, myocardial infarction and heart failure occurring during follow-up before incident AF, were mediatory factors by which the relation between WBC count and AF was (partly) explained, we additionally adjusted for these factors (Table 2). However, neither the baseline covariates; smoking and previous myocardial infarction, nor the interim covariates; myocardial infarction and heart failure during follow-up, substantively attenuated the association between WBC count and incident AF. No significant interactions between WBC count and smoking ($p=0.34$), heart failure ($p=0.34$) or myocardial infarction ($p=0.34$) were observed.

During 5-year follow-up, 140 participants (15%) died without having incident AF. To address a potential bias we computed additional models accounting for the potential competing risk of death. We found comparable risk estimates using this method; the results of the competing risk models are shown in Supplementary Table 2.

In secondary analyses we expanded the follow-up duration beyond the prespecified 5-years of follow-up, to investigate whether the found WBC-AF relation remains present during longer follow-up durations. In Supplementary Table 2 we report the results of the analyses accounting for the competing risk of death over 10-year follow-up. The observed hazards ratio during 10-year follow-up was similar to the hazard ratio observed during 5-year follow-up, however, the WBC-AF relation was not statistically significant.

Discussion

In our analysis of prospectively followed participants from a community-based sample, we observed that increased WBC count was related to incident AF during 5-years of follow-up.

Our results provide additional evidence for the relation between inflammatory markers and incident AF.

Inflammation has been associated with AF in numerous pre-clinical and clinical studies. Higher concentrations of inflammatory biomarkers like C-reactive protein and interleukin-6 have been observed in post-operative AF patients. In such cohorts, the surgery itself results in a highly increased inflammatory state.^{10,11} Others have shown that the concentration of inflammatory biomarkers is increased in patients with recurrent or incident AF.¹²

Although, focal lesions of inflammation have been found in atrial myocardium,^{13,14} the pathophysiological mechanism by which inflammation increases AF susceptibility is not well understood. One possibility is that inflammation supports substrate modification by electrical and structural remodeling of the atria, increasing the susceptibility for AF.^{13–15} Another possibility is that an increased inflammatory state induces incident AF, during systemic inflammatory conditions, systemic infections, or post-operative states.¹²

To our knowledge, WBC count has not been used to study the relation between inflammation and incident AF in the general population. WBC count is a widely available and routinely performed measure of systemic inflammation. Total WBC count represents the sum of all leucocytes; neutrophils, eosinophils, basophils, lymphocytes, monocytes and macrophages. The concentration of leucocytes increases as response to many inflammatory stimuli. In the field of cardiovascular disease, there is consistent evidence that increased WBC count is related to coronary artery disease,^{16,17} cardiovascular disease,¹⁸ stroke,¹⁹ and mortality.^{17,20–23} These associations may be mediated by smoking^{24,25} obesity,²⁶ and hypertension,^{27,28} yet the exact pathophysiological mechanism underlying these relations are not known. WBC count, as marker of systemic inflammation, may be causal or the result of cardiovascular disease.

Our study extends the current range of inflammatory biomarkers in the field of AF to WBC count, and broadens the potential application of WBC count as cardiovascular risk biomarker to AF. The relation between WBC count and AF remains after adjusting for standard AF risk factors, like age, sex, body mass index, systolic blood pressure, valvular disease, and heart failure. Additional adjustment for smoking, previous myocardial infarction, and interim myocardial infarction and heart failure did not alter this relation. Thus, AF risk factors including smoking, myocardial infarction and heart failure are unlikely to be the only mediators of this relation.

In secondary analyses, we tested whether relation between WBC and incident AF also holds true for longer follow-up durations. There may be an early relation between WBC and incident AF, but that does not prove that there is also a mid-term or long-term relation. The observed hazards ratio during 10-year follow-up was similar to that observed during 5-year follow-up, however, it was no longer statistically significant. Our results are consistent with the concept that an increased inflammatory state may induce AF. However, we acknowledge that our findings must be replicated in data sets with more events, and potentially with longer follow-up durations.

The Framingham Heart Study is a well-characterized community-based sample with extensive routine ascertainment of clinical risk factors for AF and other cardiovascular risk factors and conditions, and rigorous clinical ascertainment of incident AF. However, some limitations merit consideration. Data regarding different types of leucocytes, and other inflammatory biomarkers, like high sensitivity C-reactive protein, were not available at the 20th Cohort examination. Furthermore, serial measurements of WBC count during follow-up are not available, precluding a detailed study of the time course underlying the association between WBC count and incident AF. Thus, future studies should include WBC count and

other inflammatory biomarkers, serial measurements of WBC count, and different types of leucocytes, to gain more mechanistic information. Our study sample was modest in size and we had too few events to establish whether the association between WBC and AF occurred at a biological threshold. Although we attempted to adjust for all relevant covariates, we cannot exclude the possibility of residual confounding; unmeasured variables associated with inflammation, rather than WBC count, could account for the increased risk of incident AF. The modest sample size, together with the older age of the participants at baseline, and the competing risk of death, also limited our ability to extend our results to longer follow-up durations. African-Americans and Afrocaribbeans are known to have lower WBC counts than Caucasians.²⁹ Whether our results are generalizable to other races and ethnicities and younger ages is therefore uncertain.

The relation between WBC and incident AF suggests that further efforts to understand the mechanisms connecting inflammation and AF are indicated. Such insights may motivate increased study of anti-inflammatory therapies in an attempt to prevent AF. Lifestyle changes like smoking cessation, and weight loss can reduce inflammation. Furthermore, drugs like angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and statins have anti-inflammatory actions, which is thought one of the mechanisms by which these drugs may reduce new-onset and recurrence of AF.^{30–32}

Whether inflammation is a risk factor or a risk marker for AF requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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No. of participants at risk

WBC tertile 1	336	328	321	303	296	288
WBC tertile 2	294	290	286	277	263	250
WBC tertile 3	306	293	283	268	254	239

Figure 1.
Cumulative incidence of AF by tertile of WBC count.

Table 1

Characteristics of study participants.

Variable	Participants (n=936)
Age (years)	76±6
Women	575 (61%)
Smoker	96 (10%)
Body mass index (kg/m ²)	26.6±4.6
Systolic blood pressure (mm Hg)	147±22
Antihypertensive therapy	506 (54%)
PR interval duration (msec)	170±33
Precordial murmur ^a	67 (7%)
Heart failure	28 (3%)
Myocardial infarction	90 (10%)
White blood cell count (10 ⁹ /L) ^b	6.4 [5.6, 7.8]
Log _e White blood cell count	1.88±0.26

^a Murmur = systolic murmur at least grade 3 of 6 intensity, or any diastolic murmur.

Data presented as mean ± standard deviation, n (%), or in the case of untransformed white blood cell count^b median [25th, 75th percentile].

Table 2

Relation of white blood cell count and incident atrial fibrillation using Cox proportional regression analyses.

Variable	Log _e WBC count	Hazard ratio ^a (95% confidence interval)	p value
Age- and sex-adjusted	2.78 (1.36–5.66)		0.005
Standard AF risk factors ^b	2.22 (1.10–4.48)		0.03
Standard AF risk factors + smoking	2.33 (1.14–4.75)		0.02
Standard AF risk factors + previous myocardial infarction	2.21 (1.10–4.45)		0.03
Standard AF risk factors + interim myocardial infarction ^c	2.16 (1.07, 4.35)		0.03
Standard AF risk factors + interim heart failure ^c	2.16 (1.07, 4.39)		0.03
Standard AF risk factors + interim myocardial infarction + heart failure ^c	2.16 (1.07, 4.35)		0.03

AF = atrial fibrillation; WBC = white blood cell.

^a Hazard ratios for incident AF are shown per 1 SD increment in WBC count.

^b The standard AF risk factors are: age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, and heart failure.

^c Interim events are those events occurring after baseline, during follow-up before incident AF.