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Usefulness of High-Sensitivity C-Reactive Protein to Predict Mortality in Patients with Atrial Fibrillation (From the Atherosclerosis Risk in Communities [ARIC] Study)

José Hermida, MD, PhD[a], **Faye L. Lopez, MPH**[b], **Ramón Montes, PhD**[a], **Kunihiro Matsushita, MD, PhD**[c], **Brad C. Astor, PhD**[c], and **Alvaro Alonso, MD, PhD**[b,d]

[a]Division of Cardiovascular Sciences, Laboratory of Thrombosis and Haemostasis, Center for Applied Medical Research, University of Navarra, Pamplona, Spain

[b]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

[c]Division of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[d]Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain

Abstract

High-sensitivity C-reactive protein (hs-CRP) is a marker for risk of cardiovascular and overall mortality, but information about the association between hs-CRP and mortality in atrial fibrillation (AF) patients is scarce. A total of 293 participants of the Atherosclerosis Risk in Communities (ARIC) Study with a history of AF and available hs-CRP levels were studied. During a median time follow-up of 9.4 years, 134 participants died (46%). The hazard ratio (HR) of all-cause mortality associated with the highest vs. the lowest tertile of hs-CRP was 2.52; 95% CI 1.49–4.25 after adjusting for age, sex, history of cardiovascular diseases and cardiovascular risk factors. A similar trend was observed for cardiovascular mortality (57 events) (HR=1.90; 95% CI 0.81–4.45). CHADS2 score was also associated with all-cause and cardiovascular mortality: the adjusted HR were, respectively, 3.39 (95% CI 1.91–6.01) and 8.71, (95% CI 2.98–25.47) comparing those with CHADS2>2 versus CHADS2=0. Adding hs-CRP to a predictive model including CHADS2 score was associated with an improvement of the C-statistic for total mortality (from 0.627 to 0.677) and for cardiovascular mortality (from 0.700 to 0.718). In conclusion, high levels of hs-CRP constitute an independent marker for risk of mortality in AF patients.

Keywords

Atrial fibrillation; Cardiovascular risk factor; Reactive protein C

Corresponding Authors: José Hermida, MD, PhD, Division of Cardiovascular Sciences, Centre for Applied Medical Research (CIMA), University of Navarra, Avenida Pío XII, 55, 31008 Pamplona, Spain, Phone: +34 948194700, Fax: +34 948194716, jhermida@unav.es. Alvaro Alonso, MD, PhD, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 S 2nd St, Suite 300, Minneapolis, MN 55454, USA. Tel.: + 1 612 626 8597, fax: + 1 612 624 0315, alonso@umn.edu.

We have examined the association of C-reactive protein (CRP) plasma levels with the incidence of all-cause death and cardiovascular death in patients with atrial fibrillation (AF) in the Atherosclerosis Risk in Communities (ARIC) study, to exam whether the addition of CRP levels to the CHADS2 score (Congestive heart failure, Hypertension, Age over 75 years, Diabetes, and previous Stroke or transient ischemic attack) improves the stratification of patients in terms of risk of all-cause death and cardiovascular death.

Methods

In 1987–89, the ARIC Study recruited 15,792 men and women between 45 and 64 years of age at the baseline examination, sampled from 4 communities: Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[1] Participants underwent additional examinations in 1990–92, 1993–95 and 1996–98, and were followed throughout via annual telephone contact and hospital surveillance for incidence of cardiovascular events. High-sensitivity CRP (hs-CRP) was measured in blood samples obtained in visit 4 (1996–98). For the present analysis, therefore, we included ARIC participants who attended visit 4 and had a history of AF at that date. Participants with missing data on hs-CRP or other covariates and race other than white or African-American were excluded.

AF was ascertained as previously described.[2,3] Briefly, AF was determined from standard 12-lead ECGs conducted at each study visit and from hospitalization discharge codes. Previous validation studies have found excellent validity of hospitalization for the diagnosis of AF.[2,4] ARIC participants with ECG-based AF in any of the 4 study exams or an AF hospitalization before visit 4 were considered to have prevalent AF.

At visit 4, blood was drawn after an 8 hour fasting period from an antecubital vein with minimal trauma. Samples were processed by a standardized protocol and stored at −70 °C until assayed. Plasma levels of hs-CRP were determined by an immunophelometric assay (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The reliability coefficient in 421 blinded replicates was 0.99.[5]

At each study visit, participants reported information on smoking and use of medications, underwent a physical exam, and provided blood samples. For the present analysis, we used information collected at visit 4. Prevalent diabetes mellitus was defined as a fasting glucose level ≥ 126 mg dL^{-1}, non-fasting glucose level ≥ 200 mg dL^{-1}, or a history of diabetes. Two blood pressure measurements were taken with a random-zero sphygmomanometer and were averaged. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Body mass index was assessed as weight (kg) in a scrub suit divided by height (m) squared.

Prevalent heart failure was defined as self-reported use of heart failure medications or presence of heart failure according to Gothenburg criteria at visit 1 (baseline) or a hospitalization for heart failure (ICD-9CM code 428) before visit 4.[6] Prevalent coronary heart disease was defined according to previously published criteria using self-reported information, ECG data, and hospitalization records.[7,8]

Cohort participants, or their next of kin if the participant is deceased, are contacted by phone annually and interviewed regarding hospitalizations in the previous year. Information on each hospitalization involving cardiovascular disease, including stroke, is collected by trained abstractors. Mortality was ascertained through annual phone calls, ongoing surveillance of state health department death certificate files, search of hospital records, and linkage with the National Death Index.[2,3,7,8] Cardiovascular mortality was determined according to published criteria by a combination of a computer algorithm and physician's review using information on clinical signs and symptoms from hospital records, previous history of cardiovascular disease, data on death certificates, and interviews with the next of kin and the participant's physicians.[7]

We estimated the association of hs-CRP tertiles with all-cause death or cardiovascular death using Cox proportional hazard models. Follow-up was defined as the time between the visit 4 examination and death, end of follow-up or December 31, 2007, whichever came first. The linear trend in HRs across categories was tested by including hs-CRP as a continuous variable in the models. In an initial analysis we adjusted for CHADS2 score (as a continuous variable). A subsequent analysis adjusted additionally for sex, race (white, African-American), ARIC centers, prevalent coronary heart disease (yes/no), body mass index (continuous), smoking status (never, former, current), education (< high school, completed high school – some college, ≥college grad), use of antiplatelet medications (yes/no), anticoagulants (yes/no), and statins (yes/no), and ECG-defined left ventricular hypertrophy (yes/no). In a final analysis, we included the previous variables plus the individual components of the CHADS2 score: age (continuous), prevalent heart failure, diabetes (yes/no), systolic blood pressure (continuous), and use of antihypertensive medications (yes/no), and prevalent stroke (yes/no).

In additional analyses, we classified participants as high (≥ 2 mg/L) and low hs-CRP (< 2 mg/L). Tests of two-way multiplicative interactions were performed in regression models using cross-product terms for hs-CRP, as a continuous variable, and gender, age, race, and CHADS2 score.

The added value of hs-CRP in the prediction of mortality and other outcomes was assessed calculating c-statistics and the net reclassification improvement (NRI) in models with the CHADS2 score only and CHADS2 plus hs-CRP.[9,10]

Results

Among 11,656 ARIC participants attending visit 4, 293 (2.5%) had a history of AF and met other inclusion criteria. Of these, 114 had AF diagnosed in any study ECG and 48 at the visit 4 ECG. Median time between AF ascertainment and visit 4 was 2.9 years. Table 1 shows participants' characteristics by hs-CRP tertiles. Higher hs-CRP was associated with female sex, African-American race, higher BMI, higher prevalence of cardiovascular disease, hypertension, diabetes and smoking, and a higher CHADS2 score.

Over a median of 9.4 years of follow-up, 134 participants died (46%). hs-CRP levels were positively associated with mortality in a dose-response manner (Table 2). The fully–adjusted

HR (95% CI) for the highest tertile vs. the lowest tertile was 2.52 (1.49–4.25) (p for trend<0.0001). hsCRP values above 2.0 mg/L were associated with a HR (95% CI) of 1.59 (1.03–2.48) in the fully-adjusted model, when compared to lower hsCRP values. We observed no significant multiplicative interaction between hs-CRP and age, gender, race, or CHADS2 score.

In the analysis restricted to cardiovascular mortality (57 events), the results followed the same trend (Table 3), with hs-CRP in the highest tertile associated with higher risk compared to the lowest tertile (HR, 95% CI: 2.23, 1.09–4.57) after adjustment for CHADS2 score. Further adjustment attenuated the associations (table 3, models 2 and 3). The relationship between hs-CRP and ischemic stroke could not be properly studied due to the small number of patients with AF and not on anticoagulants who developed an ischemic stroke during follow-up (n=21).

CHADS2 score was a strong predictor of all-cause and cardiovascular mortality among AF patients. HR (95% CI) of all-cause and cardiovascular mortality in those with CHADS2>2 vs. those with CHADS2=0 was 3.39 (95% CI 1.91–6.01) and 8.71 (95% CI, 2.98–25.47), respectively. Adding hs-CRP to a predictive model with the CHADS2 score was associated with an improvement of the C-statistic for total mortality (from 0.627 to 0.677) and for cardiovascular mortality (from 0.700 to 0.718). The NRI in prediction of total mortality adding hs-CRP to a model with CHADS2 score only was 0.147 (p=0.002) (table 4), but no improvement was seen for prediction of cardiovascular mortality (NRI = −0.034, p=0.40).

Discussion

In this analysis of a prospective cohort followed for a median of 9.4 years, we found that higher hs-CRP levels were associated with increased all-cause and cardiovascular mortality in patients with AF, independent of other risk factors. Specifically, participants with hs-CRP levels in the highest tertile exhibited an incidence of all-cause or cardiovascular death approximately twice that of those in the lowest tertile. CHADS2 score was also associated with all-cause and cardiovascular mortality. hs-CRP, a classical marker of inflammation, has received increased attention in recent years given its ability to predict myocardial infarction, stroke and cardiovascular death among both apparently healthy subjects and cardiovascular patients.[11–15] However, our study is the one of the first to show a clear association between hs-CRP levels and total mortality among AF patients in a general population, even after adjustment for potential confounders. Although previous studies suggested that such a relationship exists, limited number of events, lack of adjustment for confounders, and short follow-up made it difficult to draw strong conclusions.[16,17]

In addition to the known association of CRP with cardiovascular outcomes, CRP is also associated with all-cause and cancer mortality.[18] Our results suggest that previous observations could also apply to individuals with AF although we have not been able to assess cancer mortality in our study.

We also found that hs-CRP levels improved risk classification beyond the CHADS2 score, suggesting that hs-CRP measurements might be included in the risk assessment of AF patients.

The community-based character of the ARIC study and the long follow-up period make our results directly applicable to the general population. Other strengths of our study include the availability of information on confounding variables and the quality of the outcome ascertainment. Some major limitations, however, should be highlighted. First, the limited sample size precluded addressing adequately the association of hs-CRP with incident stroke and, to a lesser extent, with cardiovascular mortality. Second, ascertainment of AF in the ARIC cohort has some limitations, such as reliance on hospital discharge codes. Nonetheless, we and others have shown previously that hospital discharge codes are sufficiently valid to identify AF events.[2,4] Finally, another potential limitation of this study is that time of AF ascertainment and hs-CRP measurement were not concurrent in many participants, thus elevated hs-CRP may be a marker of poor course in the past after AF ascertainment but not necessarily a prognostic predictor for newly identified AF patients.

The ability of the CHADS2 score as an independent predictor of mortality in patients with AF has recently been reported.[19,20] Our results are consistent with such studies and reinforce the notion that CHADS2 may be useful for assessing mortality risk in AF patients. Interestingly, we observed that incorporating hs-CRP as an additional variable in the CHADS2 improves the ability of the latter to predict mortality in AF patients.

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Table 1

Characterisitcs of study participants

Descriptive statistics of the baseline characteristics of eligible Atherosclerosis Risk in Communities (ARIC) participants with prevalent atrial fibrillation, stratified into high-sensitivity C-reactive protein tertiles, 1996–1998.

Variable	Tertiles of high-sensitivity C-reactive protein (mg/L)		
	<2.00 (n=96)	**2.00–5.99 (n=96)**	**≥6.00 (n=101)**
Age (years)*	67 (5)	67 (5)	65 (5)
Women	28%	27%	44%
Black	4%	5%	13%
Education			
< High school	17%	22%	24%
High school -college	42%	45%	48%
Grad school	42%	33%	28%
Body mass index (kg/m2)*	27 (4)	29 (6)	31 (7)
Cigarette Smoker			
Current	7%	11%	19%
Former	60%	55%	54%
Never	32%	33%	27%
Diabetes mellitus	19%	31%	37%
Systolic blood pressure (mm Hg)*	130 (20)	133(20)	128(20)
Diastolic blood pressure (mm Hg)*	70 (11)	72 (11)	68 (12)
Prevalent coronary heart disease	27%	34%	33%
Prevalent heart failure	19%	37%	46%
Prevalent stroke	6%	7%	10%
left ventricular hypertrophy by Electrocardiogram	3.%	7%	4%
Hypertension Medication	69%	80%	89%
Antiplatelet Medication	61%	72%	71%
Anticoagulant Medication	26%	31%	39%
Statin medication	16%	13%	15%

Variable	Tertiles of high-sensitivity C-reactive protein (mg/L)		
	<2.00 (n=96)	**2.00–5.99 (n=96)**	**≥6.00 (n=101)**
Time to death or end of follow-up (days)*	3296 (992)	3083 (1093)	2565 (1318)
CHADS2 score*, †	1.07 (0.97)	1.55 (1.01)	1.78 (1.15)

* mean (standard deviation)

† CHADS2: congestive heart failure, hypertension, age 75 years or older, diabetes, previous stroke/transient ischemic attack.

Table 2

High-sensitivity C-reactive protein tertiles and mortality

Relative Hazard (95% conficence interval) for death in Atherosclerosis Risk in Communities (ARIC) participants with prevalent atrial fibrillation by high-sensitivity C-reactive protein tertiles.

Variable		Tertiles of high-sensitivity C-reactive protein (mg/L)			p for trend
		<2.00 (n=96)	**2.00–5.99 (n=96)**	**≥6.00 (n=101)**	
Deaths		30 (31%)	42 (44%)	62 (61%)	-
Relative Hazard for death	Model 1	1 [Reference]	1.33 (0.83–2.13)	2.13 (1.36–3.33)	p<0.0001
	Model 2	1 [Reference]	1.26 (0.77–2.06)	2.04 (1.24–3.36)	p<0.0001
	Model 3	1 [Reference]	1.24 (0.75–2.03)	2.52 (1.49–4.25)	p<0.0001

Model 1: Cox proportional hazards model adjusted for CHADS2 score.

Model 2: Cox proportional hazards model adjusted for CHADS2 score, sex, race, center, smoking, prevalent coronary heart disease, body mass index, education, antiplatelet medication, anticoagulant medication, statins, ECG-based left ventricular hypertrophy.

Model 3: Cox proportional hazards model adjusted for age, sex, prevalent heart failure, diabetes, sistolic blood pressure, antihypertensive medications, prevalent stroke, race, center, smoking, prevalent coronary heart disease, body mass index, education, antiplatelet medication, anticoagulant medication, statins, ECG-based left ventricular hypertrophy.

Table 3

High-sensitivity C-reactive protein tertiles and cardiovascular mortality

Relative Hazard (95% conficence interval) for time to cardiovascular death in ARIC participants with prevalent atrial fibrillation by high-sensitivity C-reactive protein tertiles.

Variable		Tertiles of high-sensitivity C-reactive protein (mg/L)			p for trend
		<2.00 (n=96)	2.00–5.99 (n=96)	≥6.00 (n=101)	
Cardiovascular deaths		11 (11.46%)	17 (17.71%)	29 (28.71%)	
Relative Hazard for cardiovascular death	Model 1	1 [Reference]	1.32 (0.62–2.84)	2.23 (1.09–4.57)	0.10
	Model 2	1 [Reference]	1.19 (0.54–2.64)	1.81 (0.81–4.03)	0.14
	Model 3	1 [Reference]	1.05 (0.47–2.34)	1.90 (0.81–4.45)	0.12

Model 1: Cox proportional hazards model adjusted for CHADS2 score.

Model 2: Cox proportional hazards model adjusted for CHADS2 score, sex, race, center, smoking, prevalent coronary heart disease, body mass index, education, antiplatelet medication, anticoagulant medication, statins, ECG-based left ventricular hypertrophy.

Model 3: Cox proportional hazards model adjusted for age, sex, prevalent heart failure, diabetes, sistolic blood pressure, antihypertensive medications, prevalent stroke, race, center, smoking, prevalent coronary heart disease, body mass index, education, antiplatelet medication, anticoagulant medication, statins, ECG-based left ventricular hypertrophy.

Table 4

Risk classification by models including CHADS2 score and CHADS2 plus high-sensitivity C-reactive protein

Individuals in the unshaded diagonal boxes did not change classification with the addition of high-sensitivity C-reactive protein. Dark grey shading indicates the number of individuals who were reclassified in a desirable direction when high-sensitivity C-reactive protein was added to the CHADS2 score; light grey shading indicates individuals who were reclassified in an undesirable direction. Data in parentheses are row percents.

	Model with CHADS2	**Model with CHADS2 plus high-sensitivity C-reactive protein**		
	Predicted risk of death	**<30%**	**30–39%**	**≥40%**
Participants who died during follow-up (n=134)	<30%	80 (93)	5 (6)	1 (1)
	30–39%	6 (27)	12 (55)	4 (18)
	≥40%	0 (0)	2 (8)	24 (92)
Participants who did not die during follow-up (n=159)	<30%	23 (100)	0 (0)	0 (0)
	30–39%	13 (22)	41 (68)	6 (10)
	≥40%	0 (0)	14 (18)	62 (82)