Association of biomarkers of inflammation with hospitalization for heart failure and death in patients with atrial fibrillation

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Background: Hospitalization for heart failure and death are among the most common adverse clinical outcomes in patients with atrial fibrillation (AF). The underlying mechanisms are poorly understood.

Purpose: We hypothesised that inflammation, quantified by plasma levels of C-reactive protein (CRP) and interleukin 6 (IL-6), is independently associated with hospitalization for heart failure and death in a large, contemporary cohort of AF patients.

Methods: Patients with established AF and 65 years of age or older were enrolled in two large, prospective, multicentre cohort studies in Switzerland. Plasma levels of high-sensitivity (hs) CRP and IL-6 were measured from frozen EDTA plasma samples obtained at baseline. Using these two biomarkers, we calculated an inflammation score ranging from 0 to 4 (1 point for each biomarker between the 50th and 75th percentile, 2 points for each biomarker above the 75th percentile). We constructed multivariable Cox proportional hazards models to quantify the associations of hs-CRP, IL-6 and the inflammation score with time to first hospitalization for heart failure and time to all-cause mortality, respectively.

Results: A total of 3,784 patients with AF (median age 72 years, 28% women, 24% with a prior history of heart failure and 84% anticoagulation use at baseline) were followed for a median (interquartile range [IQR]) of 4.0 (2.9–5.1) years. The median (IQR) plasma levels of hs-CRP and IL-6 at baseline were 1.64 (0.81–3.69) mg/L and 3.42 (2.14–5.60) pg/mL, respectively. The incidence rates of hospitalization for heart failure and death were 3.04 and 2.80 per 100 person-years, respectively. After multivariable adjustment, both biomarkers were significantly associated with the risk of hospitalization for heart failure (per increase in 1 standard deviation [SD], adjusted hazard ratio [aHR] 1.22, 95% confidence interval [CI] 1.11–1.34 for log-transformed hs-CRP, and aHR 1.48, 95% CI 1.35–1.62 for log-transformed IL-6) and death (per increase in 1 SD, aHR 1.40, 95% CI 1.27–1.54 for log-transformed hs-CRP, and aHR 1.67, 95% CI 1.53–1.81 for log-transformed IL-6). Incidence rates of hospitalization for heart failure increased from 1.34 to 7.31 per 100 person-years across categories of the inflammation score (Figure 1). A strong relationship persisted after multivariable adjustment. Similar findings were observed for all-cause mortality.

Conclusions: Inflammation is a strong predictor of hospitalization for heart failure and death in patients with AF. Targeting inflammation may be a promising treatment strategy to improve outcomes in these patients at high risk for adverse outcomes.

Outcome	Inflammation score	Number of events	Number of patients	Rate per 100 person-years	Adjusted hazard ratio (95% CI)	p-value
Hospitalization for heart failure	0	75	1280	1.34	Reference category	
	1	75	779	2.40	1.32 (0.96-1.82)	0.091
	2	76	616	3.22	1.45 (1.04-2.00)	0.027
	3	79	454	4.80	2.04 (1.48-2.83)	<0.001
	4	120	521	7.31	2.43 (1.80-3.30)	<0.001
All-cause mortality	0	43	1280	0.75	Reference category	
	1	73	779	2.24	2.20 (1.50-3.21)	<0.001
	2	82	616	3.33	2.85 (1.95-4.15)	<0.001
	3	84	454	4.74	3.85 (2.64-5.60)	<0.001
	4	137	521	7.51	4.96 (3.47-7.09)	<0.001

All analyses were adjusted for age, gender, history of heart failure, history of hypertension, history of diabetes, history of stroke or transient ischemic attack, history of coronary artery disease, estimated glomerular filtration rate (MDRD), body mass index, anticoagulation use, smoking status and study cohort.

Observations in model: 3,650 (96.5% complete cases). For both outcomes, the p-value for trend was <0.001.

Figure 1