**NEOPTERIN FOR PREDICTION OF IN-HOSPITAL ATRIAL FIBRILLATION – THE “FORGOTTEN BIOMARKER” STRIKES AGAIN**

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Atrial fibrillation (AF), a cardiac arrhythmia that has reached epidemic proportions among the elderly, is associated with increased risk of stroke, heart failure and cardiovascular mortality (1). Current opinion favours the notion that multiple re-entrant circuits originating in the atria and rapidly firing atrial activity in the pulmonary veins represent key AF pathogenic mechanisms (1). However, epidemiological, anatomopathological, experimental and clinical studies suggest that inflammation may play a pivotal role in the initiation and maintenance of AF. (1-4). C-reactive protein (CRP) – a non specific marker of inflammation- has been shown to be associated with AF albeit a causal role for this biomarker has not been documented. (5)

Neopterin is another inflammatory marker that has received increasing attention as a biomarker of cellular immune activation. It is synthesized and released primarily by activated macrophages upon stimulation with interferon gamma (IFN-γ), a proinflammatory cytokine produced by Type 1 helper T (Th1) cells (6). The potential role of neopterin as a biomarker of cancer (6,7) and atherosclerotic cardiovascular events (8,9) has been highlighted in different studies. Avanzas et al (8) and Ray et al.(9) found that neopterin was a marker of risk in patients with stable angina and in those with acute coronary syndrome, respectively, whereas Zouridakis et al (10) showed that neopterin was a marker of plaque vulnerability and rapid coronary artery disease progression in coronary artery disease patients. Similarly, Adaki et al (11) showed neopterin to be associated with atheromatous plaque inflammation and instability in humans.

In this issue of the Journal of Internal Medicine, Zuo et al (12) assessed the association of plasma neopterin levels with risk of an inpatient hospital diagnosis of AF and also evaluated whether a combined assessment of neopterin and CRP could identify additional patients who were at high risk of AF. The study took advantage of large databases that included thoroughly characterised patients and controls. As described by Zuo et al (12), sensitivity analyses were performed to determine the robustness of their findings in the primary analysis, i.e. including coronary heart disease and heart failure as a dichotomous time-dependent covariate in the multivariate Cox models. To evaluate whether the combined use of neopterin and CRP provided additional information on the risk of incident AF, they looked at the joint associations of neopterin and CRP with AF risk by classifying individuals into 4 groups depending on whether these markers were above or below the median values. Furthermore, they tested model discrimination and the ability of the model to reclassify study participants by calculating the continuous net reclassification index and integrated discrimination index in logistic regression models containing the same covariates as the multivariable Cox model, with and without the two biomarkers

The main finding of the Zuo study (12) was that in both the community-based cohort and in patients with suspected stable angina pectoris, plasma neopterin was a predictor of risk of developing AF during hospital admission. The association was independent of age, gender, body mass index, CRP, renal function, heart failure, and conventional risk factors of CAD. Individuals with high concentrations of both CRP and neopterin had the highest relative risk of developing AF. Neopterin, however, appeared to be a more robust risk marker of risk of AF than CRP in these patients. The preeminent association of neopterin with AF risk suggests a role of cell-mediated immune responses in the pathogenesis of AF. Both IFN-γ-mediated cellular immune activation and increased oxidative stress linked to immune activation have been singled out as potentially important triggers of AF (13). Mechanisms such as nitric oxide dependent apoptosis and fibrosis affecting the atria have also been suggested to play a role in the development of AF (13). Neopterin activates the ROS-sensitive transcription factor NF-κB (14) another key player in inflammation related cardiovascular disease. As also reported by other authors in relation to neopterin concentrations and coronary events (8-10), the association between neopterin and AF risk was non-linear and became significant in the higher levels of neopterin distribution. Despite the interest of the observed association between neopterin and AF risk, it is important to stress that no causality between neopterin and AF has been established in the study.

Findings by Zuo et al (12), however, are important from a research perspective, as they may stimulate the development of clinical and experimental studies to investigate the pathogenesis of AF as the role of biomarkers of inflammation in this setting. Findings reported in the study may also have a clinical impact, as clinical trials may be carried out in primary care to assess the predictive usefulness of neopterin (and CRP) measurements in individuals at risk of developing AF. In my view, the Zuo study in AF patients has served another important purpose. It has highlighted the fact that neopterin –often ignored in reviews dealing with biomarkers of inflammation (16)- may have a major role in yet another cardiovascular field. Its potential role as a marker of cardiovascular risk in clinical practice has been eclipsed over the past decades by the overwhelming attention paid by clinical researchers and ‘trialists’ to CRP.(16) I presume that for experts in the field of IFN-γ-mediated cellular immune activation it will be encouraging to see a resurgence of neopterin, the “forgotten biomarker” (16). Zuo and colleagues should be congratulated for undertaking a comparative study of neopterin and CRP in this novel field, as their findings will most certainly help both advancing pathophysiological knowledge in AF and identifying practical applications for markers of inflammation in the AF realm.

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