

Role of Neopterin in Cardiovascular Medicine

To the Editor:

It is with great interest that we read the excellent review of biomarkers in cardiovascular medicine by Martin-Ventura et al.¹ They reviewed the biomarkers most commonly reported in the existing literature and assessed their links with atherogenic mechanisms, atheromatous plaque disruption, endothelial dysfunction, inflammation, oxidative stress, and thrombosis. In their scholarly review, however, the authors do not mention neopterin, a marker of macrophage activation² which over the last few years has gained particular importance due to its role in cardiovascular risk stratification.³

Neopterin is a pteridine derivative, produced by activated macrophages stimulated by interferon gamma. Studies by our group⁴⁻⁹ and others¹⁰⁻¹³ have shown that neopterin can be a useful prognostic marker in the risk stratification of patients with coronary artery disease. The serum concentration of neopterin has been shown to correlate with the presence of vulnerable atheromatous plaques⁷ and acute coronary syndrome.^{4,9-11}

High neopterin levels predict risk in patients with chronic stable angina,⁶ and in hypertensive patients without obstructive coronary disease,⁵ diabetics¹³ and patients undergoing coronariography.¹² Moreover, neopterin predicts the rapid progression of coronary disease in patients with chronic stable angina.⁸ As this marker predicts cardiovascular events independently of the extension and severity of the coronary disease,^{6,14} it is reasonable to suggest that high neopterin concentrations identify patients with a “vulnerable phenotype.”¹⁵

Given the scientific evidence accumulated in the literature over recent years, we believe that neopterin should be considered as a promising

prognostic marker that may find a practical application in the clinical setting.

Pablo Avanzas,^a Ramón Arroyo-Espiguero,^b
and Juan Carlos Kaski^c

^aÁrea del Corazón, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

^bServicio de Cardiología, Hospital Universitario de Guadalajara, Guadalajara, Spain

^cCardiovascular Biology Research Centre, St George's University of London, United Kingdom

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Response

To the Editor:

In relation to the comments made by Drs Alberto Domínguez Rodríguez et al¹ and Pablo Avanzas et al² regarding our recent review of biomarkers in vascular medicine³ we would like to respond by saying the following: firstly, we would like to thank both groups for their kind words regarding our review. We would also like to comment about us not having discussed the importance of diurnal variations of biomarkers in cardiovascular disease in this review, as well as not having mentioned the role of neopterin as a cardiovascular biological marker.

As the authors of both letters are aware, the subject of plasmatic biomarkers and cardiovascular illness is extremely broad. In PubMed there are 1485 hits when searching for “plasma biomarkers and atherosclerosis” and 8207 regarding cardiovascular disease. In an excellent review on the subject,⁴ Anderson mentions in 2005 that there are already 177 protein biomarkers associated with cardiovascular disease. The new techniques, among them proteomics, are going to provide abundant information and it can be assumed that over the next few years we will come across a plethora of potential biomarkers. Paradoxically, the number of new protein markers approved for their diagnostic use in clinical practice continues to be quite rare. In our review we decided to mention the most studied biomarkers that are involved in the development and rupture of the atherosclerotic plaque (endothelial dysfunction, inflammation, oxidative stress, proteinolysis, and thrombosis), as well as new potential biomarkers, some of which are obtained in proteomic approaches.

With regards the diurnal variation of the biomarkers in vascular disease, we are completely in agreement with the comments made by Domínguez et al.¹ As they correctly mention, the relationship between circadian and seasonal rhythms and coronary disease⁵ has been known for many years.

The variability of the plasmatic concentration of the proteins involved in the genesis of vascular damage has also been discussed by many authors. Amongst these studies it would be relevant to mention the noticeable contributions of Domínguez et al regarding circadian rhythm of PCR, CD40L, melatonin, interleukin 6, VCAM-1 and MMP-9, amongst others, and cardiovascular disease.⁶⁻⁸ Some of the proteins mentioned by them, such as PCR and CD40L have higher serum concentrations in the light phase (9.00) than in the dark phase (2.00), whilst other such as VCAM-1 show a higher serum concentration in the dark phase. For obvious reasons, the majority of clinical studies are carried out using blood samples taken in the morning and from patients who have not eaten. Although all these studies are without doubt very important for understanding the implication of the diverse biomarkers in the circadian and seasonal rhythm of cardiovascular events, their extrapolation to clinical practice is not easy, as these same authors demonstrate.

With regards the comments about the role of neopterin in cardiovascular disease from Avanzas et al,² we agree about the importance of the role that neopterin can have as a biomarker in coronary disease, as well as other biomarkers that we haven't mentioned due to lack of space (eg, PAPP-A or cystatin C, previously reviewed by this same team⁹). The contributions from the authors, in particular Prof. Kaski, regarding the role of the determination of serum neopterin in particular in acute coronary syndrome, are well known by all of us with interest in plasmatic biomarkers and cardiovascular disease. The studies by authors since their initial description in 1997,¹⁰ have made an important contribution to involving neopterin, a protein produced by macrophages activated by the interferon-gamma, as a prognostic marker in risk stratification in patients with coronary disease. Recently it has also been shown that serum concentration of neopterin can be predictive of dysfunction of the left ventricle in patients with stable chronic angina.¹¹ The authors studies have been widely acknowledged in the relevant literature and this year three excellent reviews have been carried out of the subject, which we recommend to our readers.¹²⁻¹⁴ Despite not mentioning it in our review, we hope that our comments have helped to place neopterin on the list of available biomarkers and that our respected authors do not have to ever have to say again "Neopterin: still a forgotten biomarker."¹⁵

José Luis Martín-Ventura,^a Luis Miguel Blanco-Colio,^a

José Tuñón,^b and Jesús Egido^a

^aLaboratorio de Patología Vascular, Fundación Jiménez Díaz-Universidad Autónoma, Madrid, Spain

^bServicio de Cardiología, Fundación Jiménez Díaz-Universidad Autónoma, Madrid, Spain.

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