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Editorial

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Neopterin as a Marker of In-Stent Restenosis: to Have or Have Not

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Inflammation is a critical factor in early atherosclerosis, its progression, and plaque instability[1, 2]. Neopterin, a metabolite of guanosine triphosphate, is a marker of inflammation and of immune system activation; it is synthesized by activated macrophages. The plasma neopterin level is associated with clinical presentation, angiographic complexity, and intracoronary imaging findings, including thin-cap fibroatheroma, plaque rupture, and greater plaque burden in patients with coronary artery disease[3, 4]. It has been reported by several clinical studies that major adverse cardiovascular events both in patients with stable angina pectoris and those with acute coronary syndrome can be predicted by the plasma level of neopterin[3, 5, 6]. Furthermore, it has been shown by pathologic studies that neopterin abundantly expresses within *de novo* atherosclerotic lesions in human coronary and carotid arteries[3, 7]. As mentioned above, although the effectiveness of neopterin as a marker for *de novo* plaque instability is becoming apparent (**Table 1**), its pathogenic role in restenosis is unknown still.

On this issue, Yoshiyama *et al.* revealed prospectively the close relationship between preprocedural plasma neopterin levels and major adverse cardiovascular events after coronary stent implantation in patients with stable angina pectoris[8]. This tendency was especially observed in patients with bare metal stent (BMS). Additionally, they investigated the expression of neopterin in in-stent restenosis lesions. Compared with the immunoreactivity after 1st generation drug-eluting stent (DES) implantation, immunoreactivity for neopterin was greater in the neointima after BMS implantation. Neopterin-positive cells were predominantly M1 macrophages. These results suggest that there might be differences in neopterin activities at the restenosis lesion between BMS and DES.

Some study limitations and perspective should be stated. Currently, the majority of coronary interventionalists use new generation DES; therefore, further investigation is required to assess the relationship between plasma neopterin levels and cardiovascular events in patients with that. No conclusion can be drawn from pathologic evaluation of 4 cases only. To clarify neopterin expression in the neointima after BMS and DES implantation, more cases with restenosis lesions are needed. Finally, it is still unclear by which mechanism plasma neopterin increases in BMS restenosis.

In conclusion, the present study suggests that neopterin plays an important role in neointimal formation after BMS implantation, and that the measurement of plasma neopterin levels may help in predicting cardiovascular events after stenting in patients with stable angina pectoris.

Conflict of Interest

None.

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Table 1. Neopterin and cardiovascular diseases

Authors	Subjects	Findings
Coronary artery		
Sun *et al.* [4]	81 patients with CAD	In the analyses of OCT and IVUS imaging, patients with high neopterin levels had more thin-cap fibroatheroma, microvessels, and plaque ruptures.
Avanzas *et al.* [5]	297 patients with SAP undergoing PCI	Neopterin could predict cardiovascular events during the 1-year follow-up.
Ray *et al.* [6]	3,946 patients with ACS	An elevated plasma neopterin level could identify patients at a long-term risk of death or recurrent acute coronary events.
Yoshiyama *et al.* [8]	123 patients with SAP undergoing primary coronary stenting	High preprocedural neopterin levels related to cardiovascular events in the BMS group.
Carotid artery		
Sugioka *et al.* [7]	102 patients with SAP	Plasma neopterin levels were higher in patients with complex carotid plaques than in those with noncomplex plaques.
	5 endarterectomy specimens of severe carotid stenosis with complex plaques	Expression of neopterin was high in complex carotid plaques.

CAD, coronary artery disease; OCT, optical coherence tomography; IVUS, intravascular ultrasound; SAP, stable angina pectoris; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; BMS, bare metal stent.

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