



EDITORIAL COMMENT

SCUBE 1: A novel biomarker related to platelet activation and atherothrombosis[☆]



SCUBE1 – Um novo biomarcador associado a ativação plaquetária e aterotrombose

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“First of all, forgive me for speaking to you seated, but the truth is that if I stand, I run the risk of collapsing with fear.”
– Gabriel Garcia Márquez¹

The article by Bolayır et al. on the role of SCUBE1 in the pathogenesis of late stent thrombosis presenting with ST-elevation myocardial infarction (STEMI) published in this issue of the *Journal*² sends us into the wider world of biomarkers and translational medicine, which have driven much of the research on atherothrombosis in recent years. Russell Ross’s landmark 1999 work³ on the inflammatory etiology of atherosclerosis opened a Pandora’s box for those who search within the fine structure of the highly complex processes of atherosclerotic pathophysiology for molecules that are directly or indirectly related to the mechanisms of atherosclerosis, from their genesis in inflammation to the eventual thrombotic event. However, no molecule fully accounts for an entire process, and so each biomarker has a limited ability to represent reality.⁴ This principle should be kept in mind and put into practice.

The study by Bolayır et al. aims to present the results for a new biomarker associated with late stent thrombosis

in STEMI patients. It sets out to address two important issues. The first is the importance of early assessment of stent thrombosis, a relatively rare but serious complication that has been extensively studied,^{5–7} especially with regard to the differences between bare-metal stents (BMS) and the newer drug-eluting stents (DES).^{8,9} The latter are in theory less susceptible to in-stent restenosis, even in patients with significant predisposing factors, such as diabetes.¹⁰ The authors’ second focus is platelet activation, which plays a crucial role in the progression of atherothrombosis. There is growing evidence of the importance of platelets in the atherosclerotic process and of their effects, ranging from the inflammation that initiates atheroma formation when they bind to leukocytes and endothelial cells, to platelet activation itself, due to plaque rupture or erosion, triggering coronary thrombosis.¹¹ As evidence of the importance of platelet activity, a large number of biomarkers are known to influence this process, which can be divided into circulating and membrane-associated molecules. These molecules have been particularly thoroughly studied in the context of acute ischemia.¹²

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Bolayır et al. assess this issue through the potential of a novel platelet adhesion molecule, whose complex name – signal peptide-CUB (for complement proteins C1r/C1s, Uegf and Bmp1)-EGF (for epidermal growth factor)-like domain-containing protein 1 (SCUBE1) – is somewhat intimidating for cardiologists who are unfamiliar with the latest findings in basic research.¹³ This protein is the founding member of a cell membrane-associated class of molecules known as the SCUBE family. Members of this new family have been identified in human endothelial cells and platelets.¹⁴ The SCUBE1 protein is normally stored in platelet alpha granules and translocated to the surface on thrombin activation. It is also incorporated into the growing thrombus.^{12,14}

SCUBE1 has been proposed as a novel platelet endothelial cell adhesion molecule, since particularly high serum levels are found in atherothrombotic conditions such as acute coronary syndrome and large-vessel thrombotic stroke.¹² The molecule also promotes platelet-platelet interaction and is involved in platelet adhesion to the subendothelial matrix.¹³ Moreover, deposition of SCUBE1 have been found in the subendothelial matrix of advanced atherosclerotic lesions.¹⁴ SCUBE1 blockade may even be a new antithrombotic strategy.¹⁵ All of the above evidence on this new biomarker makes it potentially attractive for the diagnosis of arterial thrombosis in medium-sized and large vessels,^{16,17} as a marker of ischemia in acute coronary syndrome,¹⁸ or even as a new therapeutic target.

This potential led the authors to proceed with the clinical study presented here. Their methodology is open to criticism, since only 40 patients with documented stent thrombosis hospitalized due to STEMI were recruited, compared to a substantially larger heterogeneous control population (n=150), consisting of patients with STEMI (n=100) and no late stent thrombosis and patients who were healthy on cardiovascular assessment (n=50). The authors acknowledge that the small sample size is a limitation that could be resolved in the future by conducting a multicenter study. Another limitation is the lack of data on which stents were used in the study population (BMS vs. DES). This information would give a more solid foundation to the study's conclusions. However, the statistical analysis does not appear to have been affected by the heterogeneity of the control group, since in all cases three groups are compared, thus maintaining the different characteristics of the study groups.

The discussion conveys the importance of platelet activation in acute coronary ischemia, as well as in other vascular conditions, such as ischemic stroke.¹⁶ Bolayır et al. are right to stress this point, since the role of platelet adhesion markers has already been demonstrated by the importance of the CD40 ligand, elevated levels of which are associated with unstable coronary artery disease.¹⁹ The authors set out to add to this knowledge in their study, in which, despite the above-mentioned limitations, they claim to have proved the relationship between late stent thrombosis and serum SCUBE1 level.

For our part, we recognize that the study has limitations, but it is headed in the right direction. As in the

quotation by Gabriel García Márquez, a writer known for his humility, we suggest that it is better to proceed with caution; with regard to SCUBE1 in the great ocean of biomarkers of atherothrombotic disease, it is better to speak while seated, since we could lose our way if we say too much. We believe that there is still much to be learned before this promising molecule can reach clinical practice.

Conflicts of interest

The author has no conflicts of interest to declare.

References

- García Márquez G. *Yo no vengo a decir un discurso*. 1st ed. New York: Vintage Español; 2010.
- Bolayır H, Kıvrak T, Güneş H, et al. The role of SCUBE1 in the development of late stent thrombosis presenting with ST-elevation myocardial infarction. *Rev Port Cardiol*. 2018;37:375–81.
- Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med*. 1999;340:115–26.
- Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem*. 2008;54:24–38.
- Cardona L, Simas A, Lousinha A, et al. Very late coronary stent thrombosis after discontinuation of antiplatelet therapy. *Rev Port Cardiol*. 2011;30:333–9.
- Seabra Gomes R, de Araujo Goncalves P, Campante Teles R, et al. Late results (>10 years) of intracoronary beta brachytherapy for diffuse in-stent restenosis. *Rev Port Cardiol*. 2014;33:609–16.
- Vieira MS, Luz A, Anjo D, et al. Triple, simultaneous, very late coronary stent thrombosis. *Rev Port Cardiol*. 2013;32:247–52.
- Barros V, Pereira M, Araujo C, et al. Use of drug-eluting versus bare-metal stents after an acute coronary syndrome in Portugal: the EURHOBOP study. *Rev Port Cardiol*. 2015;34:449–56.
- Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J*. 2015;36:3320–31.
- Ruiz-Garcia J, Teles R, Rumoroso JR, et al. Comparison between diabetic and non-diabetic patients after successful percutaneous coronary intervention for chronic total occlusions in the drug-eluting stent era. *Rev Port Cardiol*. 2015;34:263–70.
- Lindemann S, Kramer B, Seizer P, et al. Platelets, inflammation and atherosclerosis. *J Thromb Haemost*. 2007;5 Suppl 1:203–11.
- Ferroni P, Rioldino S, Vazzana N, et al. Biomarkers of platelet activation in acute coronary syndromes. *Thromb Haemost*. 2012;108:1109–23.
- Tu CF, Yan YT, Wu SY, et al. Domain and functional analysis of a novel platelet-endothelial cell surface protein, SCUBE1. *J Biol Chem*. 2008;283:12478–88.
- Tu CF, Su YH, Huang YN, et al. Localization and characterization of a novel secreted protein SCUBE1 in human platelets. *Cardiovasc Res*. 2006;71:486–95.
- Wu MY, Lin YC, Liao WJ, et al. Inhibition of the plasma SCUBE1, a novel platelet adhesive protein, protects mice against thrombosis. *Arterioscler Thromb Vasc Biol*. 2014;34:1390–8.
- Turkmen S, Eryigit U, Karaca Y, et al. Diagnostic value of plasma signal peptide-Cub-Egf domain-containing protein-1 (SCUBE-1)

- in an experimental model of acute ischemic stroke. *Am J Emerg Med.* 2015;33:262–5.
17. Dai DF, Thajeb P, Tu CF, et al. Plasma concentration of SCUBE1, a novel platelet protein, is elevated in patients with acute coronary syndrome and ischemic stroke. *J Am Coll Cardiol.* 2008;51:2173–80.
 18. Heeschen C, Dimmeler S, Hamm CW, et al. Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med.* 2003;348:1104–11.
 19. Peacock WF. Will SCUBE1 solve the ischemia marker deficit? *J Am Coll Cardiol.* 2008;51:2181–3.