Editorial

In-stent restenosis and thrombosis due to metal hypersensitivity: implications for Kounis syndrome

Ioanna Koniari, Nicholas G. Kounis, George Hahalis

Department of Cardiology, University of Patras Medical School, Patras, Greece

Correspondence to: Nicholas G. Kounis, MD, PhD. Department of Cardiology, University of Patras Medical School, Patras, Greece.
Email: ngkounis@otenet.gr.

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The metal platforms used in interventional cardiology can prevent the late luminal enlargement and induce advantageous vascular remodeling, but have failed to prevent restenosis which remains a problem due to neointimal hyperplasia. Therefore, the first and the second generation drug-eluting stents have been developed in an effort to prevent vessel restenosis. Indeed, drug-eluting stents have significantly reduced in-stent restenosis and target lesion revascularization rates compared with the bare metal stents, but a very dangerous and lethal side effect has emerged with these stents that is acute, late and especially very late stent thrombosis. The thrombus formation inside the stent lumen is the result of platelet adhesion, platelet activation by activating factors that is followed by platelet aggregation (1). This occurs because stented regions constitute an ideal substrate for foreign body reaction due to endothelial damage and dysfunction, hemorheologic changes and turbulence as well as platelet dysfunction, coagulation and fibrinolytic disturbances, at least until re-endothelialization will have been completed (2). Several important papers have been published concerning hypersensitivity toward metallic stent failure such as restenosis-thrombosis, with their authors urging for further studies to be carried out in an effort to prevent, diagnose and treat such dangerous complications. Indeed, in a recent report (3) concerning atopic patient sensitized to nickel, in-scaffold thrombosis had occurred at the mid segment of the absorb bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, California, USA) implanted in-ZES (Resolute Integrity zotarolimus-eluting stent, Medtronic, Santa Rosa, California, USA) for in-stent restenosis. Furthermore, reports that have been published recently have raised important questions about the pathophysiology of allergy-associated in-stent restenosis and thrombosis, as well as their prediction, prevention and treatment (4). The general plea, therefore, for efforts to prevent hypersensitivity-associated complications and especially stent restenosis-thrombosis should take into account the followings:

(I) The factors for stent restenosis include (5) stent underexpansion, overexpansion, malapposion, vessel tortuosity, calcification, total occlusion drug resistance, uncontrolled hypertension, diabetes, insulin resistance, genetic factors, such as the PIA polymorphism of glycoprotein IIIa, insertion/deletion polymorphism, plasma activity of angiotensin I-converting enzyme and allergy to stent components. These causes should be searched and be considered before any stent insertion;

(II) In susceptible patients following the stent implantation, blood-implant interactions are taken place and lead to complement system activation. This triggers the body's innate immune system, which leads to white blood cells infiltration (primarily neutrophils and monocytes) at the implantation site and to tissue edema. Following this, collagen fibers are deposited around the implant to form a dense, acellular, fibrous capsule that induces rapidly progressive neointimal hyperplasia and in-implant restenosis (6). On a molecular level, acute inflammation takes place with increased levels of pro-inflammatory cytokines (7). Such cytokines are excreted by neutrophils and macrophages and in the case of hypersensitivity by eosinophils and mast cells that constitute the pathophysiological basis

of Kounis hypersensitivity-associated coronary syndrome (8);

(III) The zotarolimus stent platform is made of stainless steel that is an alloy of nickel, chromium, titanium, manganese, and molybdenum. Furthermore, the so-called "cobalt chromium" and "platinum-chromium" stents have platforms that contain nickel and other metals and seems that these terms are inappropriate. The information we have obtained from the manufacturers indicates that the alloy composition of zotarolimus stent is 35% nickel, 20% chromium, 10% manganese and 35% cobalt and of everolimus stent is 55% cobalt, 20% chromium, 15% tungsten, and 10% nickel. Indeed, in the US nickel, chromium and cobalt induce allergic skin reactions in about 14%, 4%, and 9% while in Europe in about 20%, 4%, and 7% respectively (9);

(IV) The metallic scaffolds used in the bare metal and drug eluting stents counteract the main event that can occur and progress in a set frame of time, namely coronary artery restenosis. Since the majority of restenotic events occur within the first 6 months (10) and the most feared thrombotic complications of the permanent stents occur very late (beyond 1 year after implantation), the question which arises is: has any clear function a permanent stent prosthesis to be in place beyond this initial period? The bioresorbable and bioabsorbable stents have a lot advantages over the previous types of stents but have also many limitations. Recent reports have shown that bioresorbable scaffold components can induce local foreign body reactions and hypersensitivity reactions (11);

(V) Metals are ubiquitous in the surrounding environment because they are normally present in water, food and generally in the earth's crust and individuals could be easily sensitized to these. Metals can release metal ions while are embedded in the arterial orifice and are directly or indirectly in touch with the blood stream. Such anions can react with high affinity and low affinity IgE antibody receptors FCγRI, FCγRII, FCεRI and FCεRII, on platelet surface and trigger the Kounis syndrome (8). The Kounis hypersensitivity-associated acute coronary syndrome is manifesting as coronary artery spasm that can progress to myocardial damage, as acute myocardial infarction following plaque erosion of rupture and as stent thrombosis with thrombus infiltrated by eosinophils and/or mast cells. Fatal cases of Kounis syndrome have been already reported (12,13).

In order to prevent and treat all above serious consequences, it has been suggested that the FDA recommendations for coronary stent implantation should be applied to all kinds of stents including bioresorbable scaffolds (11). In order to predict and prevent such dangerous consequences these recommendations which emphasize clearly that careful history of hypersensitivity reactions with monitoring of inflammatory mediators as well as lymphocyte transformation studies to detect material hypersensitivity, before implantation, should be always considered (14).

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Footnote

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Comment on: Brugaletta S, Gori T, Low AF, *et al*. Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison: the BVS-EXAMINATION Study (bioresorbable vascular scaffold-a clinical evaluation of everolimus eluting coronary stents in the treatment of patients with ST-segment elevation myocardial infarction). JACC Cardiovasc Interv 2015;8:189-97.

References

1. Mehta SR, Yusuf S. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. J Am Coll Cardiol 2003;41:79S-88S.
2. Kounis NG, Giannopoulos S, Tsigkas GG, et al. Eosinophilic responses to stent implantation and the risk of Kounis hypersensitivity associated coronary syndrome. Int J Cardiol 2012;156:125-32.

3. Granata F, Moscarella E, Varricchio A. In-stent restenosis because of nickel hypersensitivity: a bioresorbable solution? Coron Artery Dis 2015;26:461-2.
4. Nakajima Y, Itoh T, Morino Y. Metal allergy to everolimus-eluting cobalt chromium stents confirmed by positive skin testing as a cause of recurrent multivessel in-stent restenosis. Catheter Cardiovasc Interv 2016;87:E137-42.
5. Tsigkas GG, Karantalis V, Hahalis G, et al. Stent restenosis, pathophysiology and treatment options: a 2010 update. Hellenic J Cardiol 2011;52:149-57.
6. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol 2008;20:86-100.
7. Kastellorizios M, Tipnis N, Burgess DJ. Foreign Body Reaction to Subcutaneous Implants. Adv Exp Med Biol 2015;865:93-108.
8. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med 2016;54:1545-59.
9. Almpanis GC, Tsigkas GG, Koutsojannis C, et al. Nickel allergy, Kounis syndrome and intracardiac metal devices. Int J Cardiol 2010;145:364-5.
10. Colombo A, Karvouni E. Biodegradable stents : "fulfilling the mission and stepping away". Circulation 2000;102:371-3.
11. Kounis NG, Soufras GD, Tsigkas G, et al. Bioabsorbable stent thrombosis Quo Vadis: is Kounis syndrome still present? Int J Cardiol 2014;176:305-6.
12. Brott BC, Anayiotos AS, Chapman GD, et al. Severe, diffuse coronary artery spasm after drug-eluting stent placement. J Invasive Cardiol 2006;18:584-92.
13. Salouage I, El Aidli S, Kastalli S, et al. Fatal Kounis syndrome with stent thrombosis secondary to amoxicillin/clavulanic acid use: A case report and literature review. Therapie 2016;71:535-39.
14. Review of XIENCE V Everolimus Eluting Coronary Stent System and PROMUS Everolimus Eluting Coronary Stent System: P070015. Food and Drug Administration, Silver Spring, MD; 2008. Available online: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p070015

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