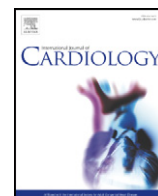




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Letters to the Editor

Absence of metal allergy in patients with very late drug-eluting stent thrombosis: A pilot study

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Stent thrombosis (ST) is a rare but devastating complication of percutaneous coronary intervention (PCI) associated with myocardial infarction and death. While ST <1 year after PCI occurs more frequently and with similar frequency after bare metal stent and drug-eluting stent (DES) implantation, very late ST >1 year after PCI appears to be more germane to DES, or at least to first-generation DES, i.e., the Cypher® sirolimus-eluting stent (SES; Cordis, Johnson & Johnson, Miami Lakes, FL) and the Taxus® paclitaxel-eluting stent (PES; Boston Scientific, Natick, MN) [1]. The mechanisms underlying very late ST with DES are poorly understood, but delayed vessel healing, chronic inflammation, incomplete endothelialization, stent malapposition, and resistance to antiplatelet agents appear to contribute to the pathogenesis [1]. Specifically, autopsy studies and intracoronary thrombus aspirates from patients with very late ST of DES have indicated the presence of hypersensitivity reactions in the stented coronary segment with infiltrating eosinophils and T lymphocytes, suggesting that delayed hypersensitivity to DES, i.e., the metallic stent platform, the drug-eluting polymer, and/or the antiproliferative drugs (sirolimus and paclitaxel), may be a prevailing mechanism [2–5]. The metallic stent platform of most stents including first-generation DES is made from 316 L stainless steel, which contains and releases sensitizing metals, e.g., nickel, chromium, and

molybdenum, and limited evidence has indicated that contact allergy to metals as determined by epicutaneous patch tests is more prevalent in patients with in-stent restenosis of bare metal stents [6,7]. It was recently also suggested that ST after DES can represent a manifestation of acute coronary syndrome caused by allergic conditions, i.e., the Kounis syndrome [8]. This specific association remains unproven and the impact of metal allergy on ST has not, to our knowledge, been reported previously. We therefore performed a small pilot study in order to assess the prevalence of metal allergy as determined by positive patch tests in patients with very late ST after DES.

Ten patients with previously implanted SES or PES presented to our institution with ST segment elevation myocardial infarction and definite very late ST as determined by the presence of intracoronary thrombus in or within 5 mm of the DES during primary PCI [9]. The baseline characteristics of patients are presented in Table 1. All were men, with age 55 ± 12.8 years, 6 had diabetes mellitus, and the culprit DES (SES: $n=5$, PES: $n=5$) was implanted 34.5 ± 18.8 months previously. No patient had a history of contact allergy or allergic contact dermatitis, apart from 1 who had previously experienced a cutaneous reaction to iodine-containing disinfectant. In 8 patients, the culprit DES had been implanted for acute myocardial infarction, and at baseline, 8 were treated with aspirin, and 3 also received clopidogrel. One patient had been noncompliant with all his medications for several days before the event and all other subjects denied noncompliance with antiplatelet therapy before admission. All patients were successfully treated by primary PCI, with implantation of new DES in 8 cases. Culprit DES fractures were not apparent at coronary angiography, thrombectomy devices were not utilized, and intracoronary ultrasound examination, optical coherence tomography or assessments of platelet aggregation and CYP genotypes were not performed. Infinite dual antiplatelet therapy was scheduled for all cases and during the following 6 months there were no deaths or new myocardial infarctions.

After we obtained informed consent, standard patch testing was performed in all patients the day after PCI, using Finn Chambers® (8 mm Epitest Ltd., Oy, Finland) on Scanpor tape® (Norgesplaster A/S, Alphen, Vennesla, Norway) and the following test substances: nickel (II) sulphate 5% in petrolatum (pet.), potassium dichromate 0.5% in pet., cobalt chloride 1% in pet., molybdenum chloride 2.5% in pet., titanium dioxide 2% in pet., manganese (II) sulphate 2% in aqua, and methylmethacrylate 2% in pet. The patch tests were applied to the

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Table 1

Baseline characteristics of patients (n = 10) with very late stent thrombosis after drug-eluting stent (DES) implantation. MI=myocardial infarction, BMI=body mass index, CABG=coronary artery bypass grafting, SES=sirolimus-eluting stent, PES=paclitaxel-eluting stent, LMS=left main stem, LAD=left anterior descending artery, Cx=circumflex artery, RCA=right coronary artery, EF=ejection fraction.

Age, years	55 ± 12.8
Male/female	10/0
BMI, kg/m ²	25.7 ± 2.7
Diabetes, n	6
Prior MI, n	8
Prior CABG, n	1
Culprit DES age, months	34.5 ± 18.8
Culprit DES, SES/PES	5/5
Target vessel, LMS/LAD/Cx/RCA	0/8/0/2
Culprit DES, number per lesion	1.7 ± 1.1
Culprit DES diameter, mm	3.00 ± 0.49
Culprit DES length, mm	23.6 ± 5.6
Postprocedure EF, %	36 ± 9

upper back and were occluded for 2 days. Readings were done on day 2, on day 3 or day 4, and on day 7 according to recommendations from the International Contact Dermatitis Research Group [10]. All patch test readings were negative.

In this small pilot study of patients with very late ST after first-generation DES, contact allergy to metals as determined by epicutaneous patch testing was absent, indicating that very late ST in this setting is not primarily determined by delayed hypersensitivity reactions to metallic stent compounds.

Very late ST after PCI with SES and PES implantation is a rare event with rates averaging 0.5% per year that has been associated with a localized in-stent hypersensitivity reaction [1–5]. Metal allergy occurs frequently in the general population, and up to 17% of women and 3% of men are considered to be allergic to nickel, and 1–3% to cobalt and chromium, although there are geographic variations, e.g., depending on regulations on nickel release from consumer products [11]. As yet, gender variations in very late ST rates have not been reported with DES or bare metal stents, which may also argue against a predominant role for metal allergy in ST. The drug-eluting synthetic polymer coatings of DES, i.e., a durable copolymer of poly-n-butyl methacrylate and polyethylenevinyl acetate for SES, and a proprietary hydrocarbon-based polyolefin derivative for PES, and/or the eluted antiproliferative drugs per se, i.e., sirolimus and paclitaxel for SES and PES, respectively, are more likely candidates to elicit allergic reactions. Although absence of reactions to methylmethacrylate in our current patch tests may be relevant to the SES polymer, the contribution of hypersensitivity to these compounds to very late ST after DES therefore requires further study [3,8]. The new generations of DES

generally avoid nickel in favour of cobalt–chromium in their strut framework, and use biocompatible, hydrophilic, and either durable (e.g., phosphorylcholine) or bioerodable (e.g., polylactid acid) polymer drug carriers that potentially may reduce hypersensitivity reactions, or no polymer at all [12]. In view of the complex pathophysiology of ST across the spectrum from acute to very late ST, however, an intracoronary stent that does not carry risk of ST may remain an elusive goal. Although we recognize the limited power and other limitations of the current study, e.g., only patients surviving a definitive ST were examined, absence of intracoronary or thrombus imaging, and the possibility that very late ST was induced by specific localized hypersensitivity reactions to DES metal compounds wall that were not detectable by epicutaneous patch testing, we conclude that metal allergy is not likely to be a primary cause of very late ST.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [13].

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