

# Viewpoint

## Hypersensitivity to drug-eluting stent and stent thrombosis: Kounis or not Kounis syndrome?

TAN Wei, CHENG Kang-lin and CHEN Qiu-xiong

**Keywords:** hypersensitivity; drug-eluting stent; stent thrombosis; Kounis syndrome

With the utilization of coronary-stents, coronary remodeling and restenosis were reduced compared with balloon angioplasty alone.<sup>1</sup> However, the risk of restenosis is still in the range of 15% to 20%. Drug-eluting stents (DES), which could release antiproliferative pharmacological agents after deployment, were designed to inhibit the response to injury reaction after bare-metal stent (BMS) implantation. As a result, target-vessel restenosis and revascularization could be reduced to rate below 10% after DES implantation.<sup>2</sup> What's more, DES have been documented to reduce the occurrence of major cardiac events from 16.4% with BMS to 7.8% with DES.<sup>3</sup> The use of DES has now increased sharply and accounts for >75% of all coronary artery stents utilized.<sup>4</sup> However, stent thrombosis (ST) after percutaneous coronary intervention is an emerging serious clinical problem in patients treated with DES. It has received considerable attention because of its high morbidity and mortality. Issues about ST are complex and controversy. Recent publications have suggested that the window of thrombotic risk in DES extends far beyond that for BMS.<sup>5,6</sup> And hypersensitivity is one of the potential factors of ST.<sup>7</sup> The concurrence of hypersensitivity reaction to DES and ST was considered as a manifestation of Kounis syndrome.<sup>8</sup>

### DRUG-ELUTING STENT AND STENT THROMBOSIS

ST was a nightmare of stent implantation since the beginning, although its rates range from 0.1% to 3.1%.<sup>9</sup> Standardized definition of ST was proposed by an academic research.<sup>10</sup> Definite ST (highest level of certainty) requires angiographic or autopsied evidence of thrombus in the segment of stent. Probable ST includes any unexplained death within 30 days after stent implantation or any MI in the territory of the stented vessel without regarding of time. Possible ST includes any unexplained death beyond 30 days until the end of follow-up. According to the time of ST, early ST refers to ST in the first 30 days; late ST defines the time interval between 1 month and 1 year after stent implantation; very late ST includes any event beyond 1 year.

Many systematic review revealed that there is no significant difference in the overall incidence of ST and the rates of protocol-defined ST up to 1 year between

BMS and DES, but significant difference was found in very late ST.<sup>11-16</sup> Evidences from autopsy, angioscope and intravascular ultrasound (IVUS) showed that delayed and impaired endothelialization plays important roles in most cases of late and very late ST, chronic inflammation and hypersensitivity reactions, stent apposition — as a result of positive arterial remodeling or stent underexpansion — and penetration of the stent into a necrotic core are other common features of adverse event.<sup>17-22</sup>

### A REAL ENTITY: HYPERSENSITIVITY TO DES

A study based on data from the FDA's Manufacturer and User Device Experience Center (MAUDE) and the Research on Adverse Drug/Device events and Reports (RADAR) project has listed 262 cases of DES (251 for CYPHER and 11 for TAXUS) implantation associated with hypersensitivity reactions.<sup>19</sup> Ninety-five percent of hypersensitivity reactions were classified as serious including events that required emergency interventions (e.g., intravenous steroids and cardiac catheterization) or hospitalization, or resulted in permanent disability, or even death. Seventeen cases were identified (14 CYPHER and 3 TAXUS) as probable or certain DES induced hypersensitivity syndromes. Clinical manifestations included non-urticarial rash, hives, dyspnea, myalgia/arthritis, itching, and blisters. Of these, four patients developed coronary thrombosis in stent and died at 4, 5, 18, and 18 months after implantation, respectively. Histological examination demonstrated intrastent eosinophilic infiltrates and poor intimal healing as late as 18 months after implantation. In one of these patients, concomitantly placed bare-metal stents were not associated with these hypersensitivity findings. Laboratory findings included eosinophilia and elevated IgE titers over five times normal for three

DOI: 10.3760/cma.j.issn.0366-6999.2009.19.036

Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510415, China (Tan W)

Department of Cardiology, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510655, China (Cheng KL)

Center of Cardiology, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, Guangdong 510120, China (Chen QX)

Correspondence to: Dr. CHEN Qiu-xiong, Center of Cardiology, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, Guangdong 510120, China (Tel: 86-20-87351238. Fax: 86-20-87351813. Email: chengkangling@126.com)

patients. Another study compared 23 autopsies of DES cases of >30 days duration with 25 matched autopsies of BMS implantation. DES cases showed greater delayed healing characterized by persistent fibrin deposition and poorer endothelialization compared with BMS.

Although the cause of DES LST is multifactorial, one of additional procedural and pathologic risk factors for LST is: local hypersensitivity (chronic inflammation) reaction characterized by lymphocytes, macrophages, and extensive eosinophilic infiltration of the intima and media.<sup>7</sup> The same was found in a case report presenting findings of a 58-year-old man who died of late stent thrombosis 18 months after receiving 2 Cypher stents for unstable angina. The autopsy showed aneurismal dilation of the stented arterial segments with a severe localized hypersensitivity reaction consisting predominantly of T lymphocytes and eosinophils. The patient did not present any clinical symptoms of hypersensitivity at the time of death, and the hypersensitivity reaction was localized to the stented arterial segment at 18 months, when the drug is completely eluted off the stent.<sup>18</sup> Hypersensitivity to DES is now regarded as real clinical entity<sup>23</sup> and may cause prolonged hypersensitivity symptoms and occasionally result in death associated with stent thrombosis.

#### POTENTIAL CAUSES OF HYPERSENSITIVITY

Hypersensitivity reactions after DES implantation could be due either to the DES itself or to medical therapy associated with stent implantation. Several components of the DES could be responsible for the hypersensitivity reaction. These include the polymer coating, the drug (rapamycin for CYPHER and paclitaxel for TAXUS), or the stainless steel. Bare-metal stents have not been demonstrated to cause hypereosinophilic, IgE-mediated reactions in a human autopsy series of over 400 stents. Hypersensitivity to bare stainless steel stents has been associated with restenosis but not thrombosis.<sup>18</sup> Drug reactions to rapamycin or paclitaxel is unlikely because pharmacokinetic studies performed in dogs and rabbits show that the drug is undetectable in the arterial wall by 60 days.<sup>24</sup> Hypersensitivity-like symptoms associated with intravenous iodinated contrast agents or ticlopidine and aspirin after a BMS implantation could not last longer than 30 days.<sup>25</sup> Thus, the most likely etiology of the hypersensitivity reaction in stent is the polymer coating of the DES. Synthetic polymers, when applied to BMS, have demonstrated both local and systemic hypersensitivity responses after implantation in one animal study.<sup>26</sup>

#### KOUNIS SYNDROME

The Kounis syndrome<sup>27</sup> was described in 1991 as the concurrence of acute coronary events with allergic or hypersensitivity reactions as well as anaphylactic or anaphylactoid reaction. Two variants of Kounis syndrome

have been described.<sup>28</sup> The type I variant, includes patients with normal coronary arteries and represents a manifestation of endothelial dysfunction; the type II variant, includes patients with culprit but quiescent preexisting atheromatous disease.

Vasoconstricting and collagen-degrading compounds are released locally and in the peripheral circulation during hypersensitivity reactions from activated mast cells. These compounds include preformed mediators as follows: arachidonic acid metabolites such as leukotrienes and thromboxane; proteolytic enzymes such as chymase and tryptase; histamine and a variety of cytokines and chemokines released during the activation of various related and interacting inflammatory cells such as macrophages, T-lymphocytes, and mast cells, which induce coronary artery spasm and/or acute myocardial infarction secondary to thrombosis. The inflammatory cells found at autopsy<sup>18</sup> to infiltrate the intima, the media, and the adventitia were the same — such as lymphocytes, plasma cells, macrophages, and eosinophils — with those participating the process of Kounis syndrome. Consequently, coincidence of hypersensitivity reaction following implantation of drug-eluting stents and stent thrombosis was considered as a manifestation of Kounis syndrome.<sup>8</sup>

#### DIFFERENT COURSE BOTH IN CLINIC AND CELLULAR LEVEL

However, both the clinical courses and the cellular level of Kounis syndrome are different from the development of hypersensitivity to DES. The clinical courses of hypersensitivity due to DES implantation are not the same as the typical cases of allergic acute coronary syndrome (ACS).<sup>29-36</sup> In allergic ACS, the duration between the onset of allergic symptoms and ACS is less than 24 hours. In contrast, the mean time from DES implantation to first symptom is 35 days, the mean duration of symptoms is more than 9.25 weeks (based on the statistic of 17 patients classified as certainly or probably due to DES, one patient had no statistic available).<sup>19</sup>

The concept of allergic ACS is based on the release of cytokines from activated mast cells and leukocytes, etc, which play an important role in atheromatous plaque erosion or rupture and induce coronary artery spasm. However, inflammatory mediators, such as histamine and arachidonic acid metabolites, have also been reported increasing in the blood or urine of patients with ACS of non-allergic aetiology.<sup>37-39</sup> Moreover, degranulated mast cells have been found abundant in the coronary plaque rupture areas of patients with recent myocardial infarction.<sup>40</sup> ACS secondary to stent thrombosis induced by hypersensitivity in response to DES is slowly developed: The hypersensitivity to the stent was most likely present at 8 months after deployment, because significant vessel enlargement and persistent positive

remodeling were found by IVUS at 8 months after DES implantation. Late stent malapposition, due to regional increase in external elastic membrane remodeling, was probably developed late after 8 months. Inflammatory destruction of the medial wall may have caused further dilation accompanied by the accumulation of fibrin between stent struts and native plaque.<sup>18</sup> All these reactions in response to DES are chronic.

In conclusion, Kounis syndrome could be considered part of hypersensitivity after DES implantation, other underlying pathogenic factors may play more significant roles in the onset of hypersensitivity to DES and lead to stent thrombosis.

#### REFERENCES

- Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994; 331: 496-501.
- Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; 349: 1315-1323.
- Babapulle MN, Joseph L, B  lisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004; 364: 583-591.
- Mueller T, ed. Stories of survival and hope mark the one million patient milestone for the CYPHER sirolimus-eluting coronary stent. Miami Lakes, FL: COMTEX, 2005.
- Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293: 2126-2130.
- McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; 364: 1519-1521.
- Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; 48: 193-202.
- Kounis NG, Kounis GN, Kouni SN, Soufras GD, Niarchos C, Mazarakis A. Allergic reactions following implantation of drug-eluting stents: a manifestation of Kounis syndrome? *J Am Coll Cardiol* 2006; 48: 592-593.
- Windecker S, Meier B. Late coronary stent thrombosis. *Circulation* 2007; 116: 1952-1965.
- Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials. *Circulation* 2007; 115: 2344-2351.
- Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006; 119: 1056-1061.
- Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; 356: 998-1008.
- Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; 356: 989-997.
- Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; 356: 1030-1039.
- Lagerqvist B, James SK, Stenestrand U, Lindb  ck J, Nilsson T, Wallentin L, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007; 356: 1009-1019.
- Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; 356: 1020-1029.
- Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 2007; 115: 2435-2441.
- Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004; 109: 701-705.
- Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting stents. A review of available cases from the research on adverse drug events and reports (RADAR) project. *J Am Coll Cardiol* 2006; 47: 175-181.
- Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; 48: 193-202.
- Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol* 2006; 47: 2108-2111.
- Mintz GS, Weissman NJ. Intravascular ultrasound in the drug-eluting stent era. *J Am Coll Cardiol* 2006; 48: 421-429.
- Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents: is it the pill or the polymer? *J Am Coll Cardiol* 2006; 47: 182-183.
- Suzuki T, Kopia G, Hayashi S, Bailey LR, Llanos G, Wilensky R, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation* 2001; 104: 1188-1193.
- Yosipovitch G, Rechavia E, Feinmesser M, David M. Adverse cutaneous reactions to ticlopidine in patients with coronary stents. *J Am Acad Dermatol* 1999; 41: 473-476.
- van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR Jr, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 1996; 94: 1690-1697.
- Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991; 45: 121-128.
- Nikolaidis LA, Kounis NG, Grandman AH. Allergic angina and allergic myocardial infarction: a new twist on an old syndrome. *Can J Cardiol* 2002; 18: 508-511.

29. Kounis GN, Hahalis G, Kounis NG. Anaphylaxis, beta blockade and the Kounis syndrome. *Paediatr Anaesth* 2008; 18: 904-905.
30. Kounis NG, Hahalis G, Theoharides TC. Coronary stents, hypersensitivity reactions, and the Kounis syndrome. *J Interv Cardiol* 2007; 20: 314-323.
31. Ioannidis TI, Mazarakis A, Notaras SP, Karpeta MZ, Tsintoni AC, Kounis GN, et al. Hymenoptera sting-induced Kounis syndrome: effects of aspirin and  $\beta$ -blocker administration. *Int J Cardiol* 2007; 121: 105-108.
32. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006; 110: 7-14.
33. Zavras GM, Papadaki PJ, Kokkinis CE, Kalokairinov K, Kouni SN, Batsolaki M, et al. Kounis syndrome secondary to allergic reaction following shellfish ingestion. *Int J Clin Pract* 2003; 57: 622-624.
34. Tavit Y, Turfan M, Türkoğlu S, Abaci A. Kounis syndrome secondary to amoxicillin/clavulanic acid use. *Int J Cardiol* 2008; 124: e4-e7.
35. Kounis NG, Kouni SN, Koutsojannis MC. Myocardial infarction after aspirin treatment, and Kounis syndrome. *J R Soc Med* 2005; 98: 296.
36. Soufras GD, Ginopoulos PV, Papadaki PJ, Zavras GM, Gouvelou-Deligianni GV, Batsolaki M, et al. Penicillin allergy in cancer patients manifesting as Kounis syndrome. *Heart Vessels* 2005; 20:159-163.
37. Clejan S, Japa S, Clemetson C, Hasabnis SS, David O, Talano JV. Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis. *J Cell Mol Med* 2002; 6: 583-592.
38. Takase B, Maruyama T, Kurita A, Uehata A, Nishioka T, Mizuno K, et al. Arachidonic acid metabolites in acute myocardial infarction. *Angiology* 1996; 47: 649-661.
39. Filipiak KJ, Tarchalska-Krynska B, Opolski G, Rdzanek A, Kochman J, Kosior DA, et al. Tryptase levels in patients after acute coronary syndromes: the potential new marker in unstable plaque? *Clin Cardiol* 2003; 26: 366-372.
40. Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 1995; 92: 1084-1088.

(Received October 27, 2008)  
Edited by WANG Mou-yue