

Metal allergic reaction in chronic refractory in-stent restenosis

Taro Saito^{a,*}, Seiji Hokimoto^b, Syuichi Oshima^b, Katsuo Noda^b,
Yasuko Kojyo^c, Kayoko Matsunaga^d

^aDepartment of Cardiology, Fukuoka Wajiro Hospital, Higashi-ku, Fukuoka City, Japan

^bDepartment of Cardiology, Kumamoto Chuo Hospital, Tainoshima, Kumamoto City, Japan

^cDepartment of Dermatology, Kumamoto Chuo Hospital, Tainoshima, Kumamoto City, Japan

^dDepartment of Dermatology, Fujita Health University Hospital, Kutsukake-cho, Toyoake City, Japan (Dermatological core lab)

Received 26 November 2007; received in revised form 6 January 2008; accepted 18 January 2008

Abstract

Objectives: This study examined the relationship between chronic refractory (CR) in-stent restenosis (ISR) and metal allergic reaction.

Background: Although drug-eluting stent reduced the restenotic event compared with bare-metal stent, the mechanism of neointimal proliferation is not clear yet; however, bare-metal stent still remains as one of the choices.

Methods: Of 128 bare-metal stent implanted patients who experienced target lesion revascularization at least once, 60 patients with the second ISR (study group) and 68 patients without the second ISR (control group) were compared in terms of result from the skin patch test for metal allergic reaction.

Results: Nickel was dominant among components of 316L stainless steel. The nickel-positive was observed in 19% (24/128) of all patients. Of 24 nickel-positive, 18 (30%) was in the study group, whereas 6 (9%) was in the control group ($P=.02$). According to multivariate analysis, the most significant predictor for CR-ISR was reference vessel diameter ($P=.0010$) followed by nickel-positive ($P=.0033$) and hyperlipidemia ($P=.0305$). The nickel-positive showed the highest odds ratio of 5.41 adjusted with confounder variables.

Conclusion: This study with the second ISR showed that nickel was a major factor for CR-ISR. Further improvement of biocompatible material is required for coronary stents and strut-coating materials even in the drug-eluting stent era.

© 2009 Elsevier Inc. All rights reserved.

Keywords:

Long term; Neointimal proliferation; Stents; Metal allergy

1. Introduction

Drug-eluting stents (DESs) have reduced restenosis in comparison with bare-metal stent (BMS) [1–7]. Although DES has dramatically contributed in the percutaneous coronary intervention (PCI), BMS is still necessary to cover limited application of DES such as intolerant patients to antiplatelet therapy. However, in-stent restenosis (ISR) ranging from 20% to 40% remains a major concern with

BMS. The mechanism of neointimal proliferation that results in ISR is not clear yet. Some studies have suggested that the contact reaction to metal material might be a factor of the neointimal proliferation [8,9]. We explored the relationship between the chronic refractory (CR)-ISR and the delayed-type hypersensitivity to the metal components of stainless steel stent (316L).

2. Materials and methods

Patients were recruited on voluntary basis from patients who received coronary stents between January 1997 and December 2001 at five centers. Each center consisted of both

* Corresponding author. Department of Cardiology, Fukuoka Wajiro Hospital, Wajirogaoka 2-2-75, Higashi-ku, Fukuoka City, 811-0213, Japan. Tel.: +81 92 608 0001; fax: +81 92 607 3051.

E-mail address: tsaito1948@mac.com (T. Saito).

Table 1
Patient baseline characteristics

	CR-ISR (n=60)	Non-CR-ISR (n=68)	P
Male	52 (87%)	52 (76%)	.097
Age	68±7.9	67±8.3	.391
DM	37 (62%)	50 (73.5%)	.151
HL	28 (46.7%)	43 (63.2%)	.060
HT	23 (38.3%)	33 (48.5%)	.246
Obesity	50 (83.3%)	64 (94.1%)	.086
Smoking	38 (63.3%)	45 (66.2%)	.737

Of 442 patients with the first TLR, 338 undertook 6-month follow-up. Of these 338, 135 (39.9%) experienced the second ISR. In those 135, 60 voluntarily participated in this research and were included into the CR-ISR group. Of 203 patients who escaped from the second ISR, 68 voluntarily participated and were included in the control group (non-CR-ISR). There was no significant difference between the two groups.

the cardiology and dermatology departments. Of the stented patients, they were eligible only if they received 316L stainless steel stent implantation and experienced TLR, which was performed for symptomatic high-grade ISR, at least once. The patients were divided into two groups at 6 months: one was the control group with patients who did not experience ISR (non-CR-ISR group) and the other one was the study group with the patients who experienced the second ISR (CR-ISR group) for high-grade ISR. The design of this research was based on the study type of “case control study” to explore predictors for occurrence of CR-ISR cases. The exclusion criteria included the bypass surgery or any surgery with metal material implant, known allergic disease, and stent implantation in branch arteries with >2.5 mm other than standard exclusion criteria for PCI.

After determination of patient voluntariness, all eligible patients were referred to the department of dermatology at each hospital and patched with the reagents of 316L stainless steel component (5% nickel sulfate, 0.5% chromate chloride, and 5% manganese oxide) prepared by the dermatological core lab, Department of Dermatology, Fujita Health University Hospital with the consent of International Contact Dermatitis Group (ICDRG) evaluation criteria. The patients visited the site dermatologist for 3- and 7-day evaluation. The test was performed in a blind fashion. The pictures of the patched sites in each patient were carefully taken by the local dermatologists and sent to the core lab. The final evaluation was performed in the core lab by the contact dermatitis specialists also in a blind manner. Only patients with the skin reaction lasted for 7 days were judged as positive.

The relation to CR-ISR cases was explored with the skin reaction for metal reagents as well as the patient baseline, lesion, and stent characteristics. The univariate and multivariate logistic regression analyses were performed to adjust influences by the confounder variables. The lesion location and characteristics were recorded according to ACC/AHA (American College of Cardiology and American Heart Association) criteria. Quantitative angiography was performed in each site. All data were monitored and

collected by each investigator, and the biostatistical analysis was done in the Kumamoto Chuo Hospital using commercially available software. All continuous values are expressed as mean±S.D., and two-sided *t* test was performed in the comparison between groups. All proportional value was expressed in percentage, and the binary distribution normalized approximation was used in the comparison between groups. The significant level of 5% was employed for the comparison test.

3. Results

3.1. Patient characteristics

Of 1371 stented and followed-up patients in the research term between January 1997 and December 2001, 442 (32.2%) patients experienced TLR at least once. Of 442 with the first TLR, 338 undertook 6-month follow-up. Of these 338, 135 (39.9%) experienced the second ISR. In those 135, 60 voluntarily participated in this research and were included into the CR-ISR group. Of 203 (60.1%) who escaped from the second ISR, 68 voluntarily participated and were included into the control group (non-CR-ISR).

Table 2
Lesion characteristics

	CR-ISR (n=60)	Non-CR-ISR (n=68)	P
Target vessel			
LAD	36 (60%)	25 (37%)	.009
LCX	11 (18%)	12 (18%)	.920
RCA	13 (22%)	31 (46%)	.004
ACC/AHA			
A	8 (13%)	4 (6%)	.149
B1	16 (27%)	21 (31%)	.560
B2	19 (32%)	35 (51%)	.024
C	17 (28%)	8 (12%)	.008
Lesion length			
<15 mm	30 (50%)	41 (60%)	.242
15–20	14 (23%)	9 (13%)	.138
20–25	3 (5%)	4 (6%)	.827
>25 mm	13 (22%)	14 (21%)	.881
RVD (mm)	2.94±0.43	3.24±0.41	.0001
Calcification			
None	46 (77%)	56 (82%)	.425
Mild	6 (10%)	4 (6%)	.386
Moderate	3 (5%)	4 (6%)	.827
Severe	5 (8%)	4 (6%)	.588
Bending			
None	36 (60%)	42 (62%)	.838
Mild	12 (20%)	16 (24%)	.630
Moderate	11 (18%)	9 (13%)	.428
Severe	1 (2%)	1 (1%)	.929

LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

LAD cases were more frequent in the CR-ISR group, while RCA cases were more frequent in the non-CR-ISR group. The case number of Type B2 lesion was significantly greater in the non-CR-ISR group than that in the CR-ISR group, and Type C lesion was significantly greater in CR-ISR group compared to the control group. The reference vessel diameter of the non-CR-ISR group was significantly greater than that in the CR-ISR group.

Table 3
Stent characteristics

	CR-ISR (n=60)	Non-CR-ISR (n=68)	P
Stent size	3.08±0.30	3.31±0.38	.0002
2.5 mm	5 (8%)	2 (3%)	.181
3 mm~	55 (92%)	66 (97%)	.181
Stent length	20.50±8.87	18.18±5.6	.087
>20 mm	23 (38%)	21 (31%)	.376
<20 mm	37	47	.376

The 316L stainless steel coronary stents used in both the groups (CR-ISR vs. non-CR-ISR) were as follows: Multilink ($n=17$ vs. $n=27$), Palmatz-Schatz ($n=18$ vs. $n=4$), Nir ($n=12$ vs. $n=30$), Gfx ($n=12$ vs. $n=7$), others ($n=1$ vs. $n=1$), respectively. Multiple use of stent was done in 15 patients with $n=12$ (38%) in the CR-ISR group vs. $n=3$ (5%) in the control group, respectively ($P=.006$). There was significant difference between groups in the stent diameter. The larger stents in diameter were used in the non-CR-ISR group compared to the CR-ISR group. These observations on multiple use and stent diameter seemed also reasonably matched to both the groups in terms of the risks.

Although slightly many cases of hyperlipidemia were observed in the non-CR-ISR group, there was no significant difference in the patient baseline characteristics between groups (Table 1).

3.2. Lesion and stent characteristics

Some significant differences between groups were observed in the lesion characteristics (Table 2). LAD cases were more frequent in CR-ISR group while RCA cases were more frequent in the non-CR-ISR group. The case number of ACC/AHA lesion Type B2 was significantly greater in the non-CR-ISR group than that in the CR-ISR group. On the contrary, the number of the Type C was significantly greater in CR-ISR group than that in the control group. The reference vessel diameter (RVD) of the non-CR-ISR group was significantly greater than that in the CR-ISR group (Table 2). The above observation seemed to give a reasonable explanation for nature of both the groups in terms of risks for PCI therapy.

The 316L stainless steel coronary stents used in both the groups (CR-ISR vs. non-CR-ISR) were as follows: Multilink ($n=17$ vs. $n=27$), Palmatz-Schatz ($n=18$ vs. $n=4$), Nir ($n=12$

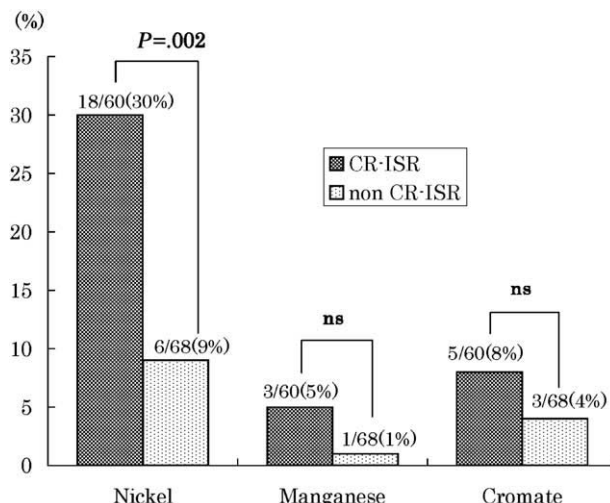


Fig. 2. Skin patch test result. The positive skin patch reaction was compared for the nickel component (24/128, 19%), the chromate component (8/128, 6%), and the manganese (4/128, 3%). In the simple comparison between CR-ISR (black bar) and non-CR-ISR (gray bar) groups, there was significant difference between groups (30% vs. 8.8%) in the nickel-positive patients ($P=.002$).

vs. $n=30$), Gfx ($n=12$ vs. $n=7$), and others ($n=1$ vs. $n=1$). Multiple use of stent was done in 15 patients with $n=12$ (38%) in the CR-ISR group vs. $n=3$ (5%) in the control group, respectively ($P=.006$).

There was significant difference between groups in the stent diameter. The larger stents in diameter were used in the non-CR-ISR group compared to CR-ISR group (Table 3). These observations on multiple use and stent diameter also seemed to reasonably match both the groups in terms of the risks.

3.3. Skin patch test result

All 128 patients divided into both groups received the skin patch reagents of the component of 316L stainless steel. The pictures of the patched site in each patient were carefully taken by the local dermatologists at 3 and 7 days after patching and being sent to core lab (Fig. 1).



Fig. 1. Patched site after 3 days (left) and 7 days (right). The evaluation was performed according to ICDRG criteria by the dermatologist in a blind manner. Only the skin reaction that continued for 7 days was considered as positive.

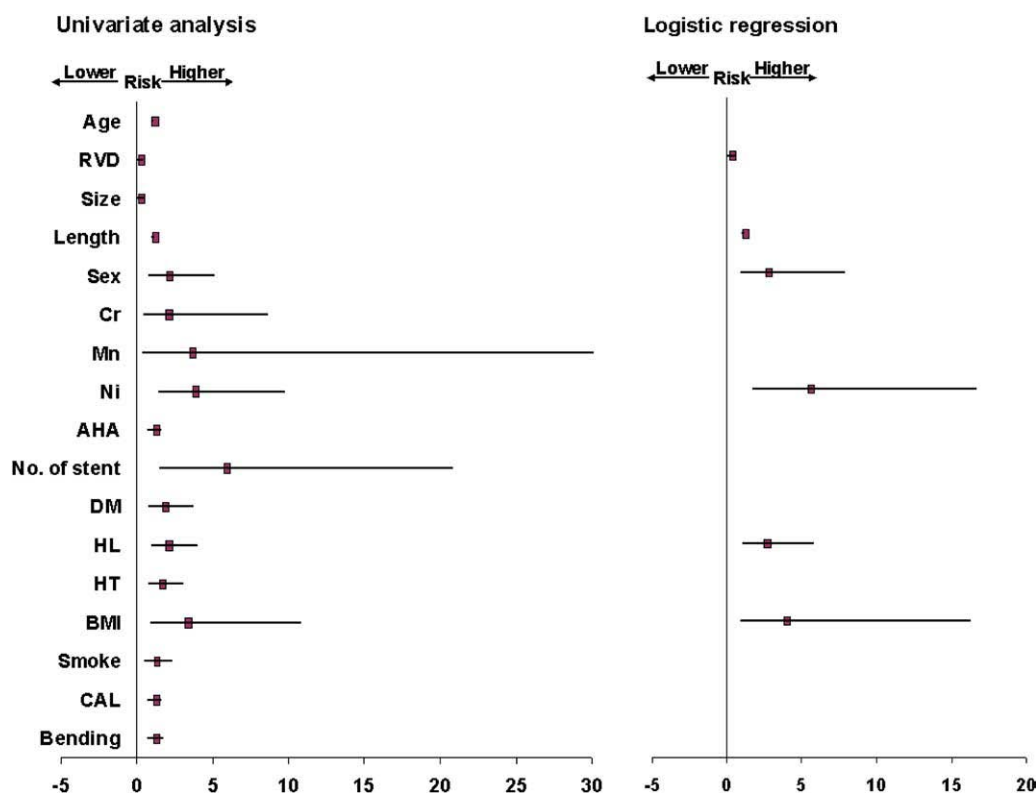


Fig. 3. Logistic regression analyses: univariate (left) and multivariate (right). The point estimate of OR and the 95% CI are illustrated. Positive or larger value of variable is considered as predictor for occurrence of CR-ISR when the OR is larger than 1.

The final evaluation was performed at the core lab by the contact dermatitis specialists in a blind manner, and only patients with the skin reaction lasted for 7 days were judged as positive. As a result, the number of positive was dominant for the nickel component (24/128, 19%), the chromate component (8/128, 6%) and the manganese (4/128, 3%) followed. In the simple comparison between CR-ISR and non-CR-ISR groups, there was significant difference between groups (30% vs. 8.8%) in the nickel-positive patients ($P=.002$; Fig. 2). The relation between CR-ISR and the nickel-positive might be broadly suggested.

3.4. Multiple variable analysis

Because some factors that were related to metal allergy as well as gender or age might also influence CR-ISR as

confounder variables, we used a logistic regression model in order to clarify the relation between metal allergy and CR-ISR more clearly by adjusting the influences of those confounder variables. After some candidate variables were determined based on the univariate analysis, we obtained the adjusted variables by the multiple stepwise regression analysis (Fig. 3).

As a result, three variables (RVD, nickel-positive, and hyperlipidemia) were demonstrated to be significantly related to occurrence of CR-ISR, and the RVD was most significant among variables ($P=.0010$; Table 4). The nickel-positive followed in significance ($P=.0033$), and the adjusted odds ratio (OR) was highest 5.41 (1.75, 16.66). We can conclude that the odds to the occurrence of CR-ISR in the nickel-positive patient were 5.41 times higher than those in nickel-negative patients.

Table 4
Multiple stepwise regression analysis

Parameters	Parameter estimate	S.E.	P	r	OR (95% CI)
Reference vessel diameter	-1.7403	0.5286	.0010	-.22	0.18 (0.06–0.49)
Stent length	0.0553	0.0318	.0813	.08	1.06 (0.99–1.12)
Male gender	0.9650	0.5550	.0821	.08	2.62 (0.88–7.79)
Nickel-positive	1.6887	0.5742	.0033	.19	5.41 (1.75–16.66)
Hyperlipidemia	0.9193	0.4250	.0305	.12	2.51 (1.09–5.77)
Obesity	1.3293	0.7452	.0744	.08	3.78 (0.88–16.28)

The result of multiple regression analysis was shown. The adjusted OR was highest in nickel-positive reaction at 5.41 (95% CI, 1.75–16.66; $P=.0033$) followed by 2.51 (95% CI, 1.09–5.77; $P=.0305$) in hyperlipidemia.

4. Discussion

The relatively stronger relationship was observed between nickel-positive patients and ISR in our study comparing to other similar studies [8–10]. We considered that our result was concentrated by higher risk with the second ISR as CR-ISR, whereas the initial restenosis was investigated in those three reports [8–10]. For example, the nickel-positive rate in our study was 19% in total, whereas the rates with initially stented patients were 5.3% to 10%. In this connection, 3.1% of manganese-positive and 6.3% of chromate-positive patients were reported in our study, whereas no positive reactions were observed [8,9]. As expected, nickel was the dominant factor among components of the 316L stainless steel. Iijima et al. [11] examined skin patch test for 65 patients who experienced first ISR and received follow-up angiography after treatment. They showed patch test-positive rate of 39% for second ISR vs. 9% for non-ISR ($P=.02$) and high OR (4.39, $P=.02$) and concluded that metal allergy may contribute to a mechanism in the recurrent ISR. In contrast to other reports, they did not find significant difference of patch test between first ISR and non-ISR (10% vs. 9%). Our study of 128 patients with first ISR demonstrated similar result of patch test for nickel (30% for CR-ISR vs. 8.8% for non-CR-ISR, $P=.002$) and highest OR of 5.41 ($P=.0033$) in nickel-positive. The mechanism of first ISR may be multifactorial and that of second ISR is strongly attributed to the tissue response to metal components, especially to nickel, which means a concern that tissue inflammation lasts as long as the release of metal components continues, resulting in resistant ISR.

This study is not intended to recommend that the patients with any possibilities of disclosure to metal, regardless of DES or BMS, should undertake patch test prior to stenting and that usage of the metal stent should be reconsidered if positive. We cannot remove the proven benefit of metal stents. We suggest that further improvement of the stent material be required as similar a platform for DES or even as a new BMS. Polymers are used in fundamental layer to deliver drug in some DES [12,13] and of some others are absorbable and finally going to be substantial BMS. BMS itself is also still necessary to cover limited application of DES. We have known that neointimal proliferation occurs in healing process responding to multifactor irritation to arteries. The wall injury in coronary arteries by pressing struts or balloon expansion, which are historically known with the balloon angioplasty [14], may be considered procedural injuries. In parallel, the foreign contact material is also considered to cause inflammatory reaction that lasts by chronic phase [15,16]. The procedural injuries occur acutely and are considered to be controlled by eluted drug from DES by 30 days when Cypher stent is implanted [17]. However, the chronic reaction to inflammation against foreign material may continue after DES completed elution of the drug. A long-term pathological analysis with autopsies shows eosinophils surrounding polymer-covered struts of

DES and delayed healing process [18,19]. We thought that CR-ISR in the patients with BMS might be caused by long-lasting hypersensitivity to metal material and that similar phenomena might happen to long-term patients with DES.

Some reports were published regarding prevention of electron transfer from metal (316L) surface into blood expecting better stent biocompatibility. According to those reports, an optimal thrombogenicity was obtained by the coating of an amorphous intrinsic semiconductor electron transfer on the surface of stainless steel [20,21].

Recently, several dermatological papers report the cytokine response by peripheral blood mononuclear cells or specific T cell [22,23], although we explored the relationship in multivariate between CR-ISR and qualitative skin reaction to metals. These quantitative studies reported optimal and toxic levels of the metal salt concentration in blood. It may give researchers a new methodology for seeking ideal material of the coronary stents and coating.

Although this study was conducted in case control form on voluntary basis, the volunteers of 60 out of 135 patients (44.4%) who experienced second TLR for ISR as CR-ISR group and 68 out of 203 patients (33.5%) who escaped second TLR as non-CR-ISR group may provide relatively tolerable research power.

5. Conclusion

Our data strongly suggested that tissue reaction to the metal component of 316L, especially nickel, may play an important role in CR-ISR.

Further improvement of biocompatibility for coronary stent material is necessary in terms of long-term safety.

References

- [1] Morice MC, Serruys PW, Sousa JE, et al, On behalf of the RAVEL Study Group. Randomized study with the sirolimus-coated BX Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773–80.
- [2] Moses JW, Leon MB, Popma JJ, et al. SIRIUS sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–23.
- [3] Schofer J, Schluter M, Gershlick AH, Wijns W, Garsia E, Schampart E, Breithart G, E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries; double blind, randomized controlled trial (E-SIRIUS). *Lancet* 2003;362:1093–9.
- [4] Schampaert E, Cohen EA, Schluter M, et al, C-CERIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;43:1110–5.
- [5] Stone GW, Ellis SG, Cox DA, et al, TAXUS IV Investigators. A polymer-based, paclitaxel eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221–31.
- [6] Hong MK, Mintz GS, Lee CW, et al, Asian Paclitaxel-Eluting Stent Clinical Trial Investigators. Paclitaxel coating reduces in-stent intimal hyperplasia in human coronary arteries: a serial volumetric

- intravascular ultrasound analysis from Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT). *Circulation* 2003;107:517–20.
- [7] Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol* 2005;45:954–9.
- [8] Hillen U, Haude M, Erbel R, Goos M. Contact allergies to metal components of the 316L steel in patients with coronary heart disease: *Mat.-wiss. U. Werkstofftech* 2002;33:747–50.
- [9] Köster R, Vieluf D, Kiehn M, Sommerauer M, Kähler J, Baladus S, Meinertz T, Hamm CW. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000;356:1895–7.
- [10] Norgaz T, Hobikoglu G, Serdar ZA, Aksu H, Alper AT, Ozer O, Narin A. Is there a link between nickel allergy and coronary stent restenosis? *Tohoku J Exp Med* 2005;206(3):243–6.
- [11] Iijima R, Ikari Y, Amiya E, Tanimoto S, Nakazawa G, Kyono H, Hatori M, Miyazawa A, Nakayama T, Aoki J, Nakajima H, Hara K. The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol* 2005;104(3):319–25.
- [12] Summary of safety and effectiveness data. Cypher™ Sirolimus-eluting OTW and RX CSS PMA#P020026.
- [13] Summary of safety and effectiveness data. TAXUS™ Express²™ Coronary Stent System. PMA#P030025.
- [14] Saito T, Date H, Taniguchi I, et al. Outcome of target sites escaping high-grade (>70%) restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1999;83:857–61.
- [15] Farb A, Weber DK, Kolodgie FD, Burke AP, Virmani R. Morphological predictors of restenosis after coronary stenting in humans. *Circulation* 2002;105:2974–80.
- [16] Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation* 2003;108:1701–6.
- [17] Klugherz BD, Llanos G, Lieuallen W, et al. Twenty-eight-day efficacy and pharmacokinetics of the sirolimus-eluting stent. *Coron Artery Dis* 2002;13:183–8.
- [18] Joner M, Finn AV, Farb A, Mont EK, Kolodgie FK, Ladich E, Kutys R, Skorija L, Gold HK, Virmani R. Pathology of drug-eluting stents in humans. Delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193–202.
- [19] Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005;112:270–8.
- [20] Rzany A, Harder C, Schaldach M. Silicon carbide as an anti-thrombogenic stent coating: an example of science-based development strategy. *Prog Biomed Res* 2000;5:168–78.
- [21] Rzany A, Harder C, Schaldach M. Smart material silicon carbide: reduced activation of cells and proteins on a-SiC: H-coated stainless steel. *Prog Biomed Res* 2001:182–94.
- [22] Sullivan KE, Cutilli J, Piliero LM, Ghavimi-Alagha D, et al. Measurement of cytokine secretion, intracellular protein expression, and mRNA in resting and stimulated peripheral blood mononuclear cells. *Clin Diagn Lab Immunol* 2000;7(6):920–4.
- [23] Minang JT, Areström I, Troye-Blomberg M, Lunderberg L, Ahlborg N. Nickel, cobalt, chromium, palladium and gold induce a mixed Th1- and Th2-cytokine response in vitro in subjects with contact allergy the respective metals. *Clin Exp Immunol* 2006;146: 417–726.