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Original article

Impact of residual platelet reactivity under clopidogrel treatment for lesions and the clinical outcome after drug-eluting stent implantation in patients with hemodialysis

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ABSTRACT

Background: Hemodialysis (HD) patients are at high risk for adverse clinical outcomes after drug-eluting stent (DES) implantation. However, the impact of residual platelet reactivity under dual anti-platelet therapy in this subset of patients remains unclear.
Methods: We enrolled 142 stable angina patients (194 lesions) treated with DES, who were taking aspirin and 75 mg clopidogrel and had undergone 8-month angiography with optical coherence tomography (OCT). OCT findings and major adverse cardiac events (MACEs) at 1 year (cardiac death, acute coronary syndrome, target lesion and vessel revascularization, and stent thrombosis) were compared between 28 HD patients and 114 non-HD patients. Responsiveness to clopidogrel was assessed by measuring P2Y12 reaction unit (PRU) at 8 months.
Results: PRU was significantly higher in HD patients than in non-HD patients ($p = 0.006$), even though proportion of cytochrome P450 2C19 genotype was equivalent. HD patients had a significantly higher rate of thrombi formation (assessed using OCT) and MACEs than non-HD patients (thrombi: $p = 0.001$; MACEs: $p = 0.0001$). The PRU value was independently associated with MACEs in both groups. The optimal cutoff values of PRU for predicting MACEs were 235 for HD patients and 259 for non-HD patients.
Conclusions: HD was associated with a high residual platelet reactivity, which may contribute to the higher incidence of MACEs after DES implantation in HD patients. HD may be a patient profile that merits a more potent anti-platelet regimen.

Introduction

Although drug-eluting stents (DES) significantly reduce restenosis compared with bare-metal stents in a wide range of populations [1], hemodialysis (HD) has created a challenging subset of patients who have massive coronary calcification and multiple lesions [2,3]. The rapid progress of percutaneous coronary intervention (PCI) devices such as the Rotablator® (Boston Scientific, Natick, MA, USA) and scoring balloon has resulted in the improvement of initial procedural success and optimal stent expansion [4,5]. Nevertheless, HD remains associated with a higher incidence of restenosis and thrombotic events after DES implantation; thus HD is an important risk factor for mortality after PCI [2,6,7] and the mechanisms underlying this association are poorly understood.

Recently, several studies have revealed that high platelet reactivity measured by VerifyNow® (Accumetrics, San Diego, CA, USA) is associated with stent thrombosis after DES implantation in patients not undergoing HD [8–10]. Meanwhile, end-stage renal dysfunction is associated with deteriorated clopidogrel effects [11–13]. Further, a few studies have revealed that HD itself may lead to high platelet reactivity [14–16] because of exposure of blood to the membrane of the dialyzer [17], heparin use [18], the platelet turnover rate, poor bioavailability, coagulation disorders, extrinsic factors such as uremia and anemia, and an altered clopidogrel metabolism [15].

However, in HD patients, the relation between residual platelet reactivity under clopidogrel use and major adverse cardiac events (MACEs) after DES implantation remains unclear. Therefore, we speculate that it is important to assess lesion characteristics and

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blood factors such as the platelet reactivity in HD patients. The aim of this study was to determine whether a high platelet reactivity to clopidogrel, as measured by VerifyNow®, is associated with MACEs after PCI with DES in HD patients compared to that in non-HD patients.

Methods

Study population

This observational study included patients who had undergone follow-up coronary angiography with optical coherence tomography (OCT) as well as platelet reactivity measured by VerifyNow® assay at 8 months. All the patients were followed up for 1 year for assessing MACE who were taking aspirin (100 mg/day) and clopidogrel (75 mg/day) for at least 12 months after DES implantation. Between April 2008 and April 2012, 665 patients with stable angina underwent elective PCI with DES (Cypher; Cordis Corp., Miami Lakes, FL, USA; TAXUS®, Boston Scientific, Natick, MA, USA; XIENCE V™, Abbott Vascular, Inc., Santa Clara, CA, USA; and Nobori, Terumo Corporation, Tokyo, Japan) for de novo native coronary lesions (822 DES). Of those, 435 patients underwent follow-up angiography at 8 months as a routine angiographic follow-up, which is widely performed in Japan. Patients with vessels >4.0 mm in diameter on angiography (n = 46) were excluded, as these vessels may be too large to remove blood flow. To ensure patient safety during OCT, patients with severe tortuous lesions, severely calcified vessels (n = 59), and left main trunk disease (n = 19) were also excluded. Of the 311 patients who were asked to undergo follow-up OCT, 209 patients agreed to undergo OCT at the follow-up angiography. Furthermore, patients who did not take clopidogrel at the follow-up angiography (n = 67) were excluded from the study. Ultimately, 142 patients (194 DES) were enrolled. OCT findings and clinical events were compared between HD and non-HD patients.

All index PCI was performed with intravascular ultrasound guidance (Boston Scientific Corp. or Volcano Corp., Rancho Cordova, CA, USA). This study was approved by the ethics committee of Kobe University.

Quantitative coronary angiographic evaluation

Quantitative coronary angiographic evaluation (QCA) was performed for the target lesion before and after PCI, and at the time of the angiographic follow-up using dedicated software (QCA-CMS 5.1; Medis, Leiden, the Netherlands). In-stent restenosis was defined as a diameter of stenosis (DS) >50% within the stented segment. In-stent late luminal loss was defined as the minimal luminal diameter immediately after PCI minus that at 8 months.

Optical coherence tomography examination

The OCT examination was performed 8 months after stenting. Frequency-domain OCT was not approved for clinical use in Japan until 2011; thus, time-domain OCT with coronary artery occlusion was used as previously reported [19]. The entire length of the stent was imaged with an automatic pullback device moving at 1 mm/s.

After 2011, frequency-domain OCT was used as previously reported [20]. The entire length of the region of interest was scanned using the integrated automated pullback device at 20 mm/s.

Optical coherence tomography analysis

Cross-sectional OCT images were analyzed at 1-mm intervals. The lumen area and stent area were measured manually. Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen, or as covered if a layer of tissue was visible over all the reflecting surfaces. Neointimal thickness was measured from the center reflection of the stent strut to the vessel-lumen border (neointimal surface or strut surface if uncovered) for each stent strut. An uncovered strut was defined as a strut with a neointimal thickness equal to 0 μm. A maximum distance of >170 μm for sirolimus-eluting stents, >164 μm for paclitaxel-eluting stents, >108 μm for everolimus-eluting stents, and >140 μm for biolimus-eluting stents between the center reflection of the strut and the adjacent vessel surface were defined as incomplete strut apposition [19,21]. To assess asymmetric stent expansion, a stent eccentricity index (SEI) was determined according to the minimum stent diameter divided by the maximum stent diameter in each cross-section. To assess the unevenness of neointimal thickness, a neointimal unevenness score (NUS) was calculated for each cross-section as the maximum neointimal thickness in one cross-section divided by the mean neointimal thickness of the cross-section. Then, the mean SEI and NUS were calculated for each stent. Thrombi were defined as irregular masses protruding into the lumen and were categorized as either erythrocyte-rich (red) thrombi (highly backscattering masses with high attenuation) (Fig. 1) or platelet-rich (white) thrombi (less backscattering, homogeneous masses with a low attenuation) [22]. To differentiate thrombi from plaque protrusions or neointimal hyperplasia, protruding masses without remarkable signal attenuation and surface irregularity were not categorized as thrombi.

Blood sampling and cytochrome P450 2C19 genotyping

We obtained blood samples from the arterial sheath at the time of follow-up angiography in order to assess the possible underlying mechanisms of the MACEs. Genomic deoxyribonucleic acid (DNA) was extracted from whole blood using the commercially available QIAamp® DNA Blood Mini Kit (Qiagen NV, Venlo, the Netherlands) according to the manufacturer's instructions. Cytochrome P450 (CYP) 2C19*2 (681G>A) or *3 (636G>A) polymorphisms were genotyped using a TaqMan® Drug Metabolism Genotyping Assay (Applied Biosystems, Foster City, CA, USA) with the 7500 Real-Time PCR System (Applied Biosystems). CYP2C19 loss of function

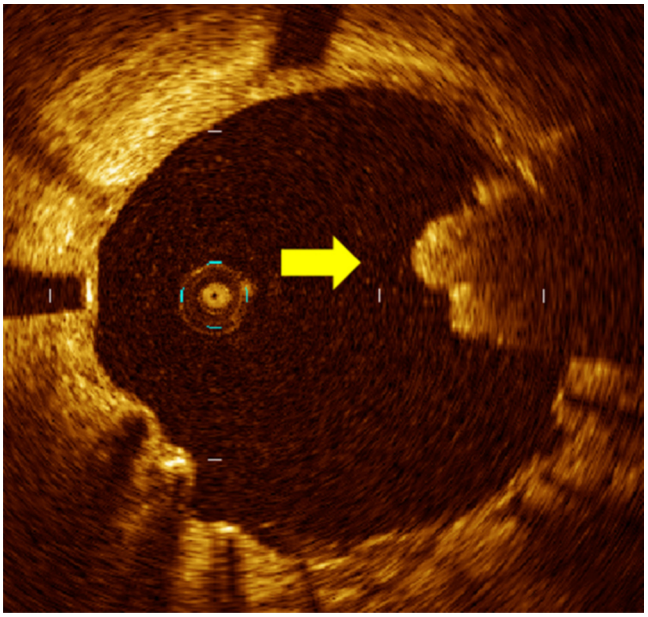

Fig. 1. Intra-stent thrombi are defined as a protruding mass beyond the stent strut into the lumen with significant attenuation behind the mass.