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Original article

# Impact of hemodialysis on local vessel healing and thrombus formation after drug-eluting stent implantation

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ABSTRACT

*Background:* Although hemodialysis (HD) is a suggested risk factor for stent thrombosis, its contribution to local vessel healing after drug-eluting stent (DES) implantation is unclear.
*Methods:* A total of 121 patients (152 lesions treated with DES) who underwent 8-month follow-up coronary angiography with optical coherence tomography (OCT) were enrolled, and the findings were compared between patients with and without HD. To match baseline differences, mid-term OCT findings of 42 propensity score-matched lesions (21 non-HD vs. 21 HD) were compared. Effects of HD on the efficacy of antiplatelet therapy were also evaluated by VerifyNow assay (Accumetrics, San Diego, CA, USA).
*Results:* Patients with HD had a significantly higher rate of thrombus formation than those without (64% vs. 33%, $p=0.007$), although the baseline parameters and lesion characteristics differed between the groups. Multivariate logistic regression analysis revealed that HD was associated with an increased risk of thrombus formation (odds ratio 5.991, 95% confidence interval: 1.972–18.199, $p=0.002$). Even after propensity-matching for patient background and balancing of angiographic and OCT variables, the risk of thrombus formation remained significantly higher in HD patients. The P2Y12-reaction unit was significantly increased after HD (Pre HD: $211\pm75$ vs. Post HD: $262\pm59$, $p=0.01$), but patients without HD showed no increase during the same elapsed time ($221\pm88$ vs. $212\pm96$, $p=0.19$).
*Conclusions:* HD is a potential risk factor for subclinical thrombus attachment after DES therapy. Systemic problems, such as residual platelet reactivity, associated with HD as well as local vessel features in HD patients might contribute to the increased incidence of thrombus attachment and subsequent onset of thrombotic event after DES implantation.
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## Introduction

Although implantation of drug-eluting stents (DES) significantly reduces restenosis compared with bare-metal stents in a wide range of patient populations [1], hemodialysis (HD) continues to be associated with an increased risk of restenosis and an unfavorable clinical outcome after DES deployment [2–5]. Because the detailed vessel response after DES implantation in patients undergoing HD therapy has not been fully elucidated, the mechanisms of such interactions remain unclear. In the present study, we assessed the relationship between HD and local vessel conditions before and after DES deployment using a large-scale single center optical coherence tomography (OCT) database pooled in the Kobe University OCT Registry. Also, to assess the possible impact of HD treatment on the efficacy of antiplatelet therapy, responsiveness to antiplatelet therapy was also evaluated using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA).

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## Materials and methods

### *Study population and methods*

Between April 2006 and April 2010, a total of 516 patients underwent elective percutaneous coronary intervention (PCI) with DES (Cypher, Cordis Corp., Miami Lakes, FL, USA; TAXUS®, Boston Scientific, Natick, MA, USA; and XIENCE V™, Abbott Vascular, Inc., Santa Clara, CA, USA) for de novo native coronary lesions (822 DES). Of those, 342 patients underwent prospectively scheduled follow-up angiography as a routine angiographic follow-up widely performed in Japan. To ensure patient safety during OCT, patients with left main trunk disease ($n = 28$), severe tortuous lesions, and severely calcified vessels ($n = 41$) were also excluded due to anticipated difficulties advancing the OCT catheters. In addition, patients with vessels greater than 4.0 mm in diameter on angiography ($n = 34$) were excluded, because these vessels might be too large to occlude blood flow. Therefore, 239 patients became candidates of the follow-up OCT registry and were asked to undergo follow-up OCT. Among these candidates, 192 patients agreed to undergo OCT at the follow-up angiography and were enrolled into the OCT registry. Furthermore, patients who did not take clopidogrel at the time of the follow-up angiography ($n = 38$) and patients who did not agree to genetic analysis ($n = 21$) were excluded from the study. A total of 133 patients (171 DES) who underwent an 8-month follow-up coronary angiography with OCT as well as genetic analysis were enrolled and the OCT findings of the lesions were compared between patients with and without HD treatment. Also, to match the potential differences in patients, lesions, and procedural characteristics, 42 propensity-score-matched lesions (21 non-HD vs. 21 HD) were queried from the overall patient population and the mid-term OCT findings were compared between patients with and without HD treatment.

The PCI procedure was performed with intravascular ultrasound guidance (Boston Scientific Corp. or Volcano Corporation, Rancho Cordova, CA, USA).

All patients were taking aspirin 100 mg/day. Clopidogrel 75 mg/day was additionally given for at least 12 months after DES implantation. This study was approved by the Ethics Committee of Kobe University and all enrolled study patients provided written informed consent. The study conformed to the tenets of the Declaration of Helsinki.

### *Coronary angiographic evaluation*

As a qualitative angiographic evaluation, coronary calcification was defined as "readily apparent densities observed within the artery wall and site of lesion as an X-ray absorbing mass," and classified as none or mild (focal densities noted only at the margin of only one side of the arterial wall); moderate (i.e. not classified as mild or severe); or severe (bulky or circulatory densities observed on both sides of the arterial wall) [6].

Quantitative coronary angiographic evaluation (QCA) was performed for the target lesion before and after the PCI and at the time of 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.

### *OCT examination*

OCT examination was performed 8 months after stenting. In this study, because frequency-domain OCT had not been approved for clinical use in Japan, time-domain OCT with coronary artery occlusion was used as previously reported [7]. The entire length of the stent was imaged with an automatic pullback device moving at 1 mm/s.

### *OCT analysis*

All images were analyzed by an independent observer blinded to the clinical presentation and lesion characteristics. Cross-sectional OCT images were analyzed at 1-mm intervals (every 15 frames).

Neointimal thickness inside each stent strut was measured. Stent area and maximum and minimum stent diameter were measured manually. Struts with a measured neointimal thickness of 0 μm were defined as uncovered struts. A maximum distance of more than 170 μm for sirolimus-eluting stents (SES), more than 164 μm for paclitaxel-eluting stents (PES), and 108 μm for everolimus-eluting stents (EES) between the center reflection of the strut and the adjacent vessel surface was defined as incomplete strut apposition [7].

To assess for asymmetric stent expansion, a stent eccentricity index (SEI) was determined by 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 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. Intra-stent thrombus was defined as a protruding mass beyond the stent strut into the lumen with significant attenuation behind the mass (Fig. 1). To differentiate thrombi from plaque protrusion or neointimal hyperplasia, we excluded protruding masses without remarkable signal attenuation and surface irregularity [8,9].

### *Blood sampling and genotyping methods*

To assess the possible underlying mechanisms of subclinical thrombus formation in HD patients, we obtained blood samples from the arterial sheath at the time of follow-up angiography. Genomic DNA was extracted from whole blood using the commercially available QIAamp™ DNA Blood Mini kit (QIAGEN N.V., Venlo, The Netherlands) according to the manufacturer's instructions. CYP2C19*2 (681G > A) or *3 (636G > A) polymorphisms were

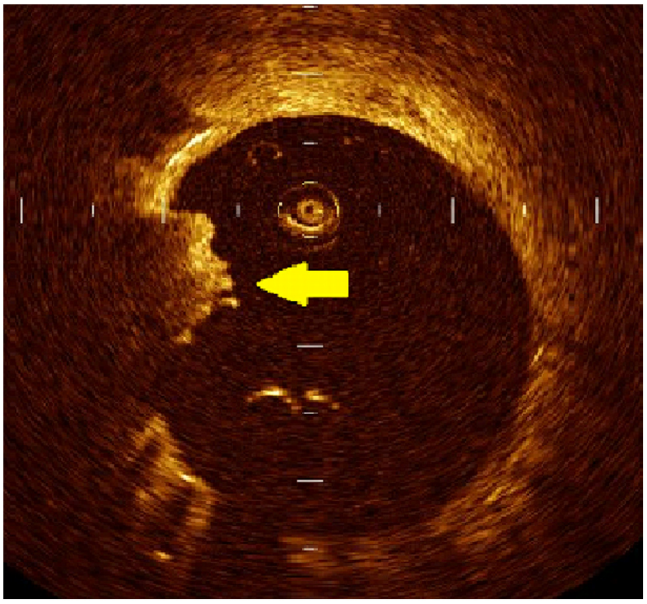

**Fig. 1.** Intra-stent thrombus was defined as a protruding mass beyond the stent strut into the lumen with significant attenuation behind the mass.

genotyped using a TaqMan™ Drug Metabolism Genotyping Assays (Applied Biosystems, Foster City, CA, USA) with the Applied Biosystems 7500 Real-Time PCR System.

Also, we performed the VerifyNow P2Y12 test, and the VerifyNow Aspirin test (Accumetrics Inc.) for 15 randomly selected patients out of a population of 42 propensity-matched patients. These tests were performed before and immediately after HD in patients treated with HD ($n = 8$) and for patients without HD ($n = 7$) at 09:00 h and 13:00 h, the times corresponding to the beginning and end, respectively, of HD treatment as previously described [10]. Briefly, the test measures platelet-induced aggregation as an increase in light transmittance and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU) and aspirin reaction units (ARU). All laboratory testing was performed by personnel blinded to patient information.

### *Mid-term clinical follow-up*

Mid-term clinical follow-up data were obtained from outpatient record reviews or telephone interviews. Target vessel revascularization was defined as any re-intervention to treat a luminal stenosis occurring in the same coronary vessel treated at the index procedure, within and beyond the target-lesion limits. All patients were followed up for at least 12 months after the index procedure.

### *Statistical analysis*

Statistical analysis was conducted with a commercially available software package (StatView ver.5.0, SAS Institute Inc., Cary, NC, USA, or PASW Statistics, version 18, SPSS, Inc., Chicago, IL, USA). Continuous variables are presented as mean ± SD. Differences in continuous parameters between the two groups were compared by an unpaired *t*-test. Categorical variables were presented using frequency counts, and intergroup comparisons were analyzed by Fisher's exact test. Because every multiple stenting was performed with overlapping, statistical analysis was performed on a patient (lesion) basis. A multivariate logistic regression analysis was performed to determine whether HD was associated with thrombus formation. Lesion-related variables inserted into the model were determined when the *p*-value was less than 0.05 between patients with and without HD in univariate analyses. Step-wise regression analysis was further performed to validate the finding as a final model. To minimize differences in baseline characteristics between the two groups and to validate the relationship between thrombus formation and HD, patients were matched in a one-to-one manner on the basis of a propensity score. The propensity score for each patient was calculated using a logistic regression model [11], which included a total of 13 variables (lesion type, bifurcation treatment, chronic total occlusion lesion treatment, use of rotablator, stent overlap, vessel disease, mean stent size, total stent length, QCA parameters including lesion length, % diameter stenosis, reference vessel diameter, and minimum lumen diameter, use of post-dilatation). According to the propensity score, patients were selected using the nearest-neighbor method. Results are reported with probability values. Outcomes including death, myocardial infarction, acute coronary syndrome, target vessel revascularization, and target lesion revascularization were compared by log-rank test between patients with and without HD treatment. Results are reported with probability value. A *p*-value of less than 0.05 was considered to be statistically significant.

## Results

### *Overall populations*

Of the 133 patients who underwent follow-up OCT, 12 were excluded due to poor image acquisition. Therefore, the data for 121 patients (SES 98, PES 51, EES 3) were analyzed in the present study. Compared with the HD patients, non-HD patients comprised more men, and were more likely to have dyslipidemia, be current smokers, CTO lesions, and have a longer total stent length. HD patients were more likely to have diabetes mellitus, moderate/severe calcification, and require rotablation, and had greater follow-up % diameter stenosis than non-HD patients (Tables 1 and 2). As for the 8-month OCT analysis of the overall population, 22,896 struts in 2858 cross-sections were analyzed. Mean minimum stent area was similar between the two groups. There was no significant difference in mean neointimal thickness, % uncovered struts, or % malapposed struts between lesions of patients treated with and those without HD. Lesions of HD patients, however, showed a smaller mean SEI with an increased incidence of intra-stent thrombus than those without HD (64% vs. 33%, $p = 0.007$; Table 3). After adjustment for demographic and angiographic differences, lesions of HD patients had a 6-fold higher risk of in-stent thrombus formation compared to lesions of those without HD (Table 4). With regard to major adverse cardiac events, HD patients had more incidences of acute coronary syndrome during the follow-up period than those without HD (median: 426 days; Table 5).

### *Propensity-matched population*

To match the baseline differences in patients, we compared the OCT findings between lesions with and without HD among 42 propensity-score-matched lesions (21 non-HD lesions vs. 21 HD lesions). Patient, lesion, or procedural characteristics did not significantly differ between the two groups (Tables 1 and 2). Based on the OCT analysis, mean stent area was similar between the two groups. Mean neointimal thickness, % neointimal area, % uncovered struts, and % malapposed struts were not significantly different between lesions of patients treated with and without HD (Table 3).

**Table 1**
Baseline patient characteristics before and after propensity score-matched population.

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | HD ($n = 25$) | Non-HD ($n = 96$) | *p*-Value | HD ($n = 21$) | Non-HD ($n = 21$) | *p*-Value |
| Baseline characteristics | | | | | | |
| Age (years) | 69.16 ± 6.67 | 69.99 ± 9.38 | 0.67 | 69.7 ± 7.0 | 70.2 ± 10.9 | 0.88 |
| Male sex, *n* (%) | 16 (64%) | 79 (82%) | 0.047 | 14 (69%) | 12 (57%) | 0.48 |
| Hypertension, *n* (%) | 21 (84%) | 78 (81%) | 0.75 | 17 (80%) | 17 (80%) | 0.78 |
| Dyslipidemia, *n* (%) | 3 (12%) | 63 (65%) | 0.0001 | 8 (38%) | 8 (38%) | 0.15 |
| Diabetes mellitus, *n* (%) | 16 (64%) | 35 (36%) | 0.01 | 13 (61%) | 11 (52%) | 0.60 |
| Smoker, *n* (%) | 3 (12%) | 42 (43%) | 0.0034 | 3 (15%) | 6 (28%) | 0.37 |
| *2 carriers, *n* (%) | 11 (46%) | 40 (41%) | 0.19 | 7 (33%) | 7 (33%) | 0.44 |
| *3 carriers, *n* (%) | 6 (26%) | 23 (23%) | 0.82 | 5 (25%) | 8 (38%) | 0.72 |

Values are presented as mean ± SD or percentages of patients. HD, hemodialysis.

**Table 2**
Baseline lesion and procedural characteristics before and after propensity score-matched population.

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | HD ($n=28$) | Non-HD ($n=124$) | $p$-Value | HD ($n=21$) | Non-HD ($n=21$) | $p$-Value |
| Coronary artery | | | | | | |
| Left anterior descending, $n$ (%) | 11 (44%) | 47 (48%) | 0.65 | 10 (47%) | 11 (52%) | 0.75 |
| Left circumflex artery, $n$ (%) | 7 (28%) | 14 (14%) | 0.11 | 7 (33%) | 3 (14%) | 0.14 |
| Right coronary artery, $n$ (%) | 7 (28%) | 35 (36%) | 0.42 | 4 (19%) | 7 (33%) | 0.29 |
| Type of lesion | | | | | | |
| B2/C, $n$ (%) | 13 (52%) | 51 (53%) | 0.92 | 9 (42%) | 10 (47%) | 0.75 |
| Moderate/severe calcification | 12 (48%) | 18 (18%) | 0.0026 | 9 (42%) | 7 (33%) | 0.40 |
| Chronic total occlusion, $n$ (%) | 2 (8%) | 24 (25%) | 0.06 | 2 (9%) | 4 (19%) | 0.37 |
| Bifurcation lesion, $n$ (%) | 9 (36%) | 32 (33%) | 0.80 | 8 (38%) | 6 (28%) | 0.51 |
| Procedural characteristics | | | | | | |
| Total number of stents, $n$ | 28 | 145 | | 23 | 30 | |
| Sirolimus-eluting stent, $n$ | 17 (60%) | 91 (62%) | 0.21 | 15 (65%) | 17 (56%) | 0.33 |
| Paclitaxel-eluting stent, $n$ | 9 (32%) | 53 (36%) | 0.64 | 6 (26%) | 13 (43%) | 0.10 |
| Everolimus-eluting stent, $n$ | 2 (7%) | 1 (0.6%) | 0.12 | 2 (8%) | 0 (0%) | 0.22 |
| Total stent length (mm) | 24.52 ± 10.76 | 36.58 ± 21.39 | 0.0074 | 25.19 ± 11.31 | 29.19 ± 20.63 | 0.44 |
| Stent size (mm) | | | | | | |
| 2.5 | 8 (28%) | 48 (33%) | 0.32 | 7 (30%) | 12 (40%) | 0.11 |
| 2.75 | 1 (3%) | 3 (2%) | 0.82 | 1 (4%) | 2 (6%) | 0.54 |
| 3.0 | 13 (46%) | 59 (40%) | 0.46 | 11 (47%) | 9 (30%) | 0.53 |
| 3.5 | 6 (21%) | 33 (22%) | 0.90 | 4 (17%) | 6 (20%) | 0.70 |
| Maximum inflation pressure (atm) | 14.96 ± 2.90 | 14.48 ± 3.36 | 0.49 | 14.85 ± 3.08 | 13.81 ± 4.89 | 0.41 |
| Post dilatation, $n$ (%) | 8 (32%) | 48 (50%) | 0.10 | 7 (33%) | 7 (33%) | 0.99 |
| Overlap stent, $n$ (%) | 7 (28%) | 30 (31%) | 0.75 | 6 (28%) | 3 (14%) | 0.25 |
| Rotablation, $n$ (%) | 8 (32%) | 4 (4%) | 0.0001 | 6 (28%) | 2 (9%) | 0.11 |
| Quantitative coronary angiography | | | | | | |
| Lesion length (mm) | 9.93 ± 5.15 | 10.98 ± 6.13 | 0.43 | 10.05 ± 5.31 | 9.02 ± 4.69 | 0.50 |
| Reference diameter (mm) | 2.44 ± 1.24 | 2.31 ± 1.18 | 0.64 | 2.45 ± 1.34 | 2.70 ± 2.21 | 0.65 |
| Minimum lumen diameter | | | | | | |
| Before PCI (mm) | 0.61 ± 0.37 | 0.53 ± 0.38 | 0.38 | 0.58 ± 0.37 | 0.71 ± 0.37 | 0.37 |
| After PCI (mm) | 2.25 ± 0.37 | 2.32 ± 0.41 | 0.44 | 2.21 ± 0.31 | 2.23 ± 0.37 | 0.80 |
| Follow-up (mm) | 1.77 ± 0.58 | 1.87 ± 0.59 | 0.44 | 1.68 ± 0.56 | 1.50 ± 0.74 | 0.36 |
| % diameter stenosis | | | | | | |
| Before PCI (%) | 71.81 ± 15.20 | 75.57 ± 16.99 | 0.31 | 72.48 ± 16.39 | 67.85 ± 15.23 | 0.34 |
| After PCI (%) | 13.06 ± 7.58 | 12.61 ± 7.24 | 0.78 | 13.59 ± 7.10 | 12.79 ± 6.44 | 0.70 |
| Follow-up (%) | 35.32 ± 22.81 | 25.03 ± 19.61 | 0.02 | 36.96 ± 23.67 | 36.54 ± 29.97 | 0.95 |
| Acute gain (mm) | 1.63 ± 0.37 | 1.78 ± 0.49 | 0.05 | 1.62 ± 0.37 | 1.57 ± 0.47 | 0.66 |
| Late loss (mm) | 0.48 ± 0.61 | 0.45 ± 0.53 | 0.77 | 0.52 ± 0.65 | 0.66 ± 0.63 | 0.49 |

Values are presented as mean ± SD or percentages of patients.
HD, hemodialysis; PCI, percutaneous coronary intervention.

Despite the lack of a significant difference in local OCT findings, intra-stent thrombus was more frequently observed in lesions of patients with HD than in those without HD (61% vs. 19%, $p=0.004$) with a tendency toward a greater NUS in lesions of patients with than those without HD (Table 3). Mid-term clinical follow-up data (median: 421days) were also obtained for the propensity-matched population. Two deaths and five acute coronary syndrome events were observed in the HD patients and one myocardial infarction occurred among the non-HD patients. Eight patients in the HD group and four patients in the non-HD group required target vessel revascularization (Table 5). All target vessel revascularization events were related to in-stent or edge restenosis of DES.

**Table 3**
Eight-month follow-up optical coherence tomography data before and after propensity score-matched population.

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | HD ($n=28$) | Non-HD ($n=124$) | $p$-Value | HD ($n=21$) | Non-HD ($n=21$) | $p$-Value |
| Mean total no of struts ($n$) | 179.37 ± 88.82 | 204.97 ± 105.15 | 0.27 | 170.42 ± 64.01 | 157.94 ± 79.05 | 0.58 |
| Minimum stent area ($mm^2$) | 5.28 ± 1.70 | 5.31 ± 1.81 | 0.94 | 4.87 ± 1.40 | 5.12 ± 1.85 | 0.63 |
| Minimum lumen area ($mm^2$) | 3.65 ± 1.44 | 3.83 ± 1.76 | 0.63 | 3.38 ± 1.21 | 3.42 ± 1.56 | 0.93 |
| Mean stent eccentricity index | 0.87 ± 0.03 | 0.89 ± 0.03 | 0.02 | 0.88 ± 0.03 | 0.89 ± 0.04 | 0.12 |
| Mean neointimal unevenness score | 1.86 ± 0.21 | 2.04 ± 0.51 | 0.29 | 1.96 ± 0.40 | 1.79 ± 0.19 | 0.09 |
| % of neointimal area (%) | 16.97 ± 8.21 | 15.49 ± 13.64 | 0.61 | 15.96 ± 8.46 | 21.58 ± 14.74 | 0.14 |
| Mean neointimal thickness (μm) | 152 ± 6.6 | 153 ± 12.3 | 0.95 | 141 ± 6.4 | 191 ± 13.9 | 0.14 |
| Frequency of uncovered struts (%) | 3.21 ± 3.95 | 6.78 ± 13.36 | 0.51 | 3.88 ± 8.99 | 1.46 ± 2.81 | 0.26 |
| Frequency of malapposed struts (%) | 0.99 ± 2.03 | 1.43 ± 2.73 | 0.69 | 0.32 ± 1.13 | 0.42 ± 1.46 | 0.81 |
| Thrombus (%) | 64 | 33 | 0.007 | 61 | 19 | 0.004 |

Values are presented as mean ± SD or percentages of patients. HD, hemodialysis.

**Table 4**
Multivariate logistic regression analyses to identify factors associated with thrombus formation in overall population. Model 1 includes vessel-related variables with p value less than 0.05 between patients with and without HD in univariate analyses. Model 2 shows results by step-wise regression analysis.

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *p*-Value | Odds ratio | 95% CI | *p*-Value |
| Haemodialysis | 7.157 | (2.102–24.369) | 0.002 | 5.991 | (1.972–18.199) | 0.002 |
| Moderate/severe calcification | 0.162 | (0.042–0.618) | 0.008 | 0.230 | (0.075–0.704) | 0.010 |
| Multiple stenting | 0.915 | (0.226–3.705) | 0.900 | – | – | – |
| Total stent length | 1.021 | (0.985–1.057) | 0.253 | – | – | – |
| Rotablation | 1.271 | (0.22–7.352) | 0.789 | – | – | – |
| Mean stent eccentricity index | 0.001 | (0–363.192) | 0.301 | – | – | – |

**Table 5**
Eight-month clinical outcomes before and after propensity score-matching.

| | Before matching | | | | After matching | | | |
|---|---|---|---|---|---|---|---|---|
| | HD *N* = 25 | Non-HD *N* = 96 | All *N* = 121 | *p*-Value (Log-rank) | HD *N* = 21 | Non-HD *N* = 21 | All *N* = 42 | *p*-Value (Log-rank) |
| Death, *n* (%) | 2(8) | 0(0) | 2(1.7) | 0.053 | 2(9.5) | 0(0) | 2(4.8) | 0.157 |
| Myocardial infarction, *n* (%) | 0(0) | 1(1) | 1(0.8) | 0.615 | 0(0) | 1(4.8) | 1(2.4) | 0.329 |
| Acute coronary syndrome, *n* (%) | 5(20) | 5(5.2) | 10(8.3) | 0.030 | 5(23.8) | 2(9.5) | 7(16.7) | 0.230 |
| Target vessel revascularization, *n* (%) | 9(36) | 13(13.5) | 22(18.2) | 0.127 | 8(38.1) | 4(19) | 12(28.6) | 0.331 |
| Target lesion revascularization, *n* (%) | 9(36) | 13(13.5) | 22(18.2) | 0.127 | 8(38.1) | 4(19) | 12(28.6) | 0.331 |

HD, hemodialysis.

*Blood sampling and genotyping results in propensity-matched population*

The percentage of patients with CYP2C19 loss of function polymorphisms was comparable between the two groups. The efficacy of clopidogrel significantly decreased immediately after HD treatment in patients with HD ($p = 0.01$; Fig. 2a), while no decrease in efficacy was observed in patients without HD during the same time period ($p = 0.19$; Fig. 2b). The efficacy of aspirin did not change in patients treated with HD ($p = 0.82$; Fig. 3a) or in those without HD ($p = 0.66$) during the 4-h interval examined (Fig. 3b).

## Discussion

The findings of the present study indicated the following. (1) In the overall population, patients with HD showed greater

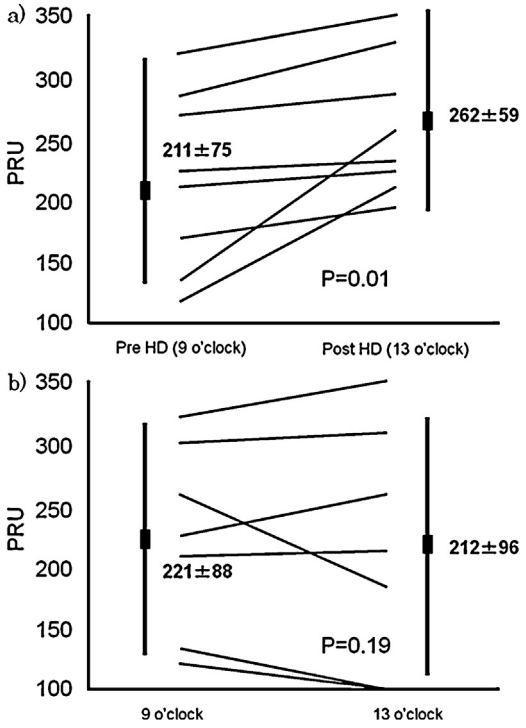


**Fig. 2.** Time course of P2Y12-reaction units (PRU) before and after hemodialysis (HD) (a) Comparison of PRU between Pre HD (9 o'clock) and Post HD (13 o'clock) in patients with HD. The efficacy of clopidogrel was significantly decreased before and after HD treatment in patients with HD. (b) Comparison of PRU between 9 and 13 o'clock in patients without HD treatment. The efficacy of clopidogrel was not deteriorated in patients without HD treatment. Values are presented as mean ± SD.

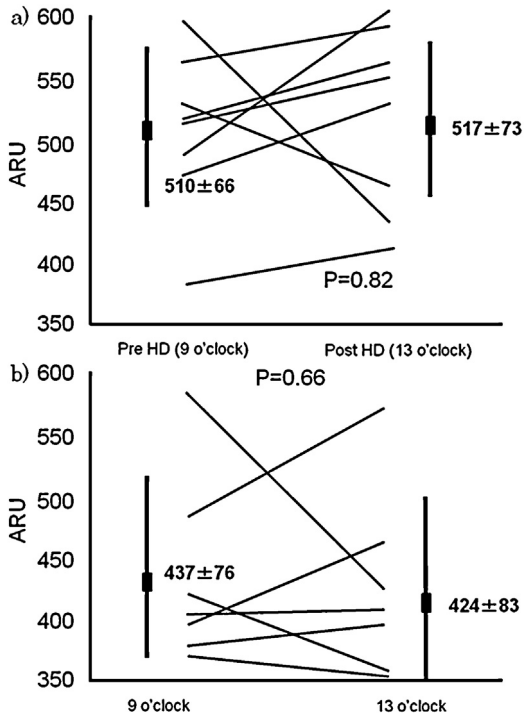


**Fig. 3.** Time course of aspirin-reaction unit (ARU) before and after hemodialysis (HD). (a) Comparison of ARU between Pre HD (9 o'clock) and Post HD (13 o'clock) in patients with HD treatment. The efficacy of aspirin was not significantly deteriorated before or after HD treatment in patients with HD treatment. (b) Comparison of ARU between 9 and 13 o'clock in patients without HD treatment. The efficacy of aspirin was not deteriorated in patients without HD. Values are presented as mean ± SD.

asymmetric stent expansion with an increased incidence of intra-stent thrombus than in patients without HD. Multivariate logistic regression analyses revealed that the risk of thrombus formation was approximately 6-fold higher in patients with HD than in those without HD. (2) Incidence of acute coronary syndrome during follow-up period was higher in HD patients than non-HD patients. (3) In the propensity-matched population, despite comparable baseline characteristics, intra-stent thrombus remained significantly higher in lesions with HD than in those without HD, with a tendency toward a greater NUS than non-HD patients. (4) The efficacy of clopidogrel measured by VerifyNow was significantly decreased after HD treatment in patients with HD, while no alteration was observed in patients without HD during the same period.

Renal dysfunction is an important risk factor for the increased incidence of death and cardiovascular events [12,13]. Although DES substantially reduces the incidence of in-stent restenosis compared with bare metal stents, HD remains a risk factor for an increased incidence of restenosis and major adverse clinical events after DES implantation [14–17]. A recent Japanese nationwide registry [The Registry of Stent Thrombosis for Review and Reevaluation (RESTART)] revealed that HD is independently associated with an increased incidence of late stent thrombosis [18]. Nevertheless, the detailed mechanisms of such relation between HD therapy and increased adverse events are poorly understood.

In this study, DES implanted in HD patients had a significantly higher incidence of subclinical thrombus than those in non-HD patients. In general, patients with HD therapy were more likely to have multiple coronary risk factors and prone to advanced atherosclerosis with diffuse severe calcification than non-HD patients. Previous investigators speculated that such patient background and progressed lesion characteristics might blunt the efficacy of DES rather than HD therapy itself. Indeed, in the overall population of the present study, lesions in patients undergoing HD were more severely calcified than lesions of patients without HD. Also, greater asymmetric stent expansion, probably due to advanced atherosclerosis, was observed in HD lesions on follow-up OCT images, despite greater use of rotablation performed for HD lesions than non-HD lesions. We previously reported that the incidence of thrombus attachment is associated with total stent length and mean SEI in a recent clinical OCT study based on 55 patients treated with SES [8]. Therefore, we speculate that these patients' background and lesion characteristics with asymmetric stent expansion in HD patients might explain the somewhat increased incidence of thrombus attachment in the overall population treated with HD.

Various factors potentially contribute to the formation of thrombus within DES-treated lesions such as stent length, the frequency of uncovered struts, stent eccentricity, and uneven neointimal coverage [8] and the presence of CYP2C19 loss-of-function polymorphisms. In the present study, it is noteworthy that the higher incidence of thrombus attachment remained significant after matching to reduce bias and confounding factors related to multiple differences. Therefore, we speculated that, aside from such patient and lesion characteristics, HD therapy itself also has a potential impact on thrombus formation after DES implantation. Several previous studies reported the possibility that HD activates platelet function by increasing shear stress through the HD dialyzer or repetitive heparin use [19]. Therefore, in this study we performed VerifyNow P2Y12 and aspirin tests to assess the efficacy of dual antiplatelet therapy for randomly selected patients from each group. We found that the efficacy of clopidogrel deteriorated significantly immediately after HD treatment in patients treated with HD, while no alteration was observed in patients without HD during the same period. There are several possible explanations for this observation. First, platelet cells might be activated when blood passes through a dialyzer. Second, sudden hypovolemic changes induced by HD might activate platelet cell function through activation of the sympathetic nervous system [19–22]. Finally, in addition to platelet cell activation by HD, consumption of platelet cells by enhanced platelet aggregation and subsequent reactive platelet cell production might explain the somewhat decreased efficacy of clopidogrel. In general, HD treatment can reduce the number of platelet cells due to enhanced platelet aggregation induced by increased shear stress through the HD dialyzer or heparin use. As a result, patients that undergo HD might have greater number of platelet cells left unaffected by clopidogrel, leading to deterioration of the clopidogrel efficacy in those patients.

Considering the management against the deterioration of anti-platelet therapy, taking clopidogrel and aspirin immediately after HD procedure or using more potent, rapid, and consistent antiplatelet drugs could be potential therapeutic options. Administration of prasugrel or ticagrelor immediately after HD treatment may be effective for inhibiting the aggregation function of newly recruited platelet cells that are unexposed to antiplatelet therapy.

## Limitations

The present study has several limitations. First, this was a non-randomized, retrospective observational study based on a relatively limited sample size. Although we used propensity scoring and matching to adjust for multiple baseline differences, propensity methods can only account for the measured variables. Therefore, it is possible that patients with HD therapy had inherently more diseased vessels in ways that we could not measure. Also, as with any observational study, we cannot prove cause-and-effect relations. Therefore, it remains unclear whether HD treatment further increases the incidence of thrombus formation in patients receiving DES. Second, this study only examined SES, PES, and EES without any comparison with bare-metal stents or other DES. Finally, the clinical relevance of our findings remains unclear, warranting a study involving a larger population with a longer follow-up period.

## Conclusion

HD is a potential risk factor for subclinical thrombus attachment after DES therapy due to local vessel features in HD patients. Considering the comparable results from the quantitative OCT evaluation of the propensity-matched patients, systemic problems, such as alteration of platelet function through HD might contribute to the increased incidence of thrombus attachment after DES implantation. A large-scale study with longer-term follow-up is warranted to further validate our findings.

## Conflict of interest

None declared.

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## References

[1] Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
[2] Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza Jr JP, Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.
[3] Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U,

Grube E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
[4] McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
[5] Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, Nishikawa H, Hiasa Y, Muramatsu T, Meguro T, Inoue N, Honda H, Hayashi Y, Miyazaki S, Oshima S, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987–95.
[6] Fujimoto H, Nakamura M, Yokoi H. Impact of calcification on the long-term outcomes of sirolimus-eluting stent implantation. Circ J 2012;76:57–64.
[7] Matsumoto D, Shite J, Shinke T, Otake H, Tanino Y, Ogasawara D, Sawada T, Paredes OL, Hirata K, Yokoyama M. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. Eur Heart J 2007;28:961–7.
[8] Otake H, Shite J, Ako J, Shinke T, Tanino Y, Ogasawara D, Sawada T, Miyoshi N, Kato H, Koo BK, Honda Y, Fitzgerald PJ, Hirata K. Local determinants of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography. JACC Cardiovasc Interv 2009;2:459–66.
[9] Ikenaga H, Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Miura F, Nakama Y, Dai K, Ohtani T, Ohi K, Miki T, Nakamura M, Kishimoto S, Sumimoto Y, Kihara Y. Longitudinal extent of lipid pool assessed by optical coherence tomography predicts microvascular no-reflow after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. J Cardiol 2013;62:71–6.
[10] Malinin A, Pokov A, Spergling M, Defranco A, Schwartz K, Schwartz D, Mahmud E, Atar D, Serebruany V. Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12(R) rapid analyzer: the VERIfy Thrombosis risk ASsessment (VERITAS) study. Thromb Res 2007;119:277–84.
[11] D'Agostino Jr RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–81.
[12] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
[13] Yoda S, Nakanishi K, Tano A, Kasamaki Y, Kunimoto S, Matsumoto N, Sato Y, Hirayama A. Risk stratification of cardiovascular events in patients at all stages of chronic kidney disease using myocardial perfusion SPECT. J Cardiol 2012;60:377–82.
[14] Ota T, Umeda H, Yokota S, Miyata S, Takamura A, Sugino S, Hayashi K, Ishiki R, Takeichi Y, Iwase M, Inagaki H, Murohara T. Relationship between severity of renal impairment and 2-year outcomes after sirolimus-eluting stent implantation. Am Heart J 2009;158:92–8.
[15] Hassani SE, Chu WW, Wolfram RM, Kuchulakanti PK, Xue Z, Gevorkian N, Suddath WO, Satler LF, Kent KM, Pichard AD, Weissman NJ, Waksman R. Clinical outcomes after percutaneous coronary intervention with drug-eluting stents in dialysis patients. J Invasive Cardiol 2006;18:273–7.
[16] Ishio N, Kobayashi Y, Takebayashi H, Iijima Y, Kanda J, Nakayama T, Kuroda N, De Gregorio J, Kouno Y, Suzuki M, Haruta S, Komuro I. Impact of drug-eluting stents on clinical and angiographic outcomes in dialysis patients. Circ J 2007;71:1525–9.
[17] Syed AI, Ben-Dor I, Collins SD, Gonzalez MA, Gaglia Jr MA, Torguson R, Satler LF, Suddath WO, Pichard AD, Lindsay J, Waksman R. Sirolimus-eluting stents versus paclitaxel-eluting stents in patients with chronic renal insufficiency. J Interv Cardiol 2010;23:33–9.
[18] Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T, Mitsudo K, Miyazaki S, Yamaguchi T, Hiyoshi E, Nishimura E, Isshiki T, Investigators R. Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: Observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation 2010;122:52–61.
[19] Gritters M, Borgdorff P, Grooteman MP, Schoorl M, Bartels PC, Tangelder GJ, Nube MJ. Platelet activation in clinical haemodialysis: LMWH as a major contributor to bio-incompatibility. Nephrol Dial Transplant 2008;23:2911–7.
[20] Matsuo T, Matsuo M, Kario K, Suzuki S. Characteristics of heparin-induced platelet aggregates in chronic hemodialysis with long-term heparin use. Haemostasis 2000;30:249–57.
[21] Charvat J, Konig J, Blaha J. Is heparin responsible for enhanced platelet aggregation after haemodialysis. Nephron 1986;44:89–91.
[22] Borm JJ, Krediet R, Sturk A, ten Cate JW. Heparin versus low molecular weight heparin K 2165 in chronic hemodialysis patients: a randomized cross-over study. Haemostasis 1986;16(Suppl. 2):59–68.