The incidence of in-stent restenosis after drug-eluting stent implantation in patients on chronic hemodialysis

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Abstract

Background: Recently, drug-eluting stents have been widely adopted rather than bare-metal stents in patients on chronic hemodialysis (HD) based on the extrapolation of data from patients on non-HD. However, whether DES implantation is associated with a reduced rate of in-stent restenosis (ISR) is unclear. We investigated the incidence of ISR and its predictors in patients on HD after drug-eluting stent implantation.

Methods and Results: We analyzed 194 consecutive patients (331 lesions) on HD who underwent follow-up angiography after drug-eluting stent implantation. ISR was observed in 74 lesions (22.4%). Angiographically, the relative incidence of AHA/ACC type C lesion was increased (47% vs. 32%; P=0.043), the minimal lumen diameter (MLD) before DES implantation was smaller (0.82±0.49 vs. 0.97±0.45mm; P<0.01) and the lesion length (LL) was increased (30.2±16.1 vs. 24.4±12.1mm; P=0.023) in lesions with ISR compared to those without ISR. The rate of rotational atherectomy use was also increased in lesions with ISR compared to those without ISR (50% vs. 25%; P<0.01). In a multivariate analysis, the MLD before drug-eluting stent implantation (odds ratio [OR] =0.50, 95% confidence interval [CI] 0.27-0.91, P=0.024), LL (OR=1.02, 95% CI 1.00-1.04, P=0.030) and the use of rotational atherectomy (OR=2.71, 95% CI 1.55-4.72, P<0.01) were independent predictors of ISR. The incidence of ISR was similar between lesions treated with the first-generation (25.8%) and the second-generation DESs (20.4%).

Conclusion: ISR was observed in 74 lesions (22.4%). A small MLD, long LL and the use of rotational atherectomy were independent predictors of ISR after drug-eluting stent implantation in patients on HD. There was no significant difference in ISR rate between the first- and the second-generation drug-eluting stents.

Introduction

Cardiovascular disease is the principal cause of death in patients on hemodialysis (HD)1–3. Coronary artery disease is common in HD patients, and percutaneous coronary intervention (PCI) has been shown to be more effective than medical therapy in such patients4. However, although initial success rate is high both in HD and non-HD patients, relatively high restenosis rate in the follow-up period has been noted in HD patients5.

Recently, drug-eluting stents (DESs) have been widely adopted rather than bare-metal stents in HD patients based on the extrapolation of data from non-HD patients. Indeed, previous studies in non-HD patients have shown that DESs reduce the rate of repeat revascularization compared with bare-metal stents, and this superiority of DESs over bare-metal stents is preserved in patients with moderate renal insufficiency6,7. However, whether DES implantation is associated with a reduced incidence of in-stent restenosis (ISR) in HD patients is less well defined. Moreover, although a meta-analysis of 33 randomized trials in non-HD patients showed that implantation of the second-generation DESs did not reduce the risk
of repeat revascularization compared with the first-generation DESs\(^8\), data on the incidence of ISR after PCI using the second-generation DESs in HD patients are scarce.

In the present study, we investigated the incidence of ISR and its predictors in HD patients after DES implantation. We also compared the incidence of ISR between the first- and the second-generation DESs.

**Methods**

**Study population**

From January 2007 to December 2017, consecutive HD patients who underwent DES implantation and follow-up angiography at 8 to 12 months after PCI at Kansai Medical University were retrospectively selected and analyzed. The exclusion criteria were survivors of sudden cardiac death, cardiogenic shock, emergent PCI, ST segment elevation myocardial infarction, intolerance to antiplatelet drugs, ISR after DES implantation, severe valvular heart disease, and candidates for renal transplantation. The ethical committee approved our database search. Because of the retrospective nature of the study, written informed consent from the patients was waived. However, the patients who refused enrollment when contacted for follow-up were excluded.

All PCIs were performed in accordance with concurrent guidelines, and the stent choice was left to the discretion of the operator. All stents were commercially available. Before February 2010 all patients were treated with the first-generation DESs. The first-generation DESs used were a sirolimus-eluting stent (SES; Cypher\™; Cordis Corp, Johnson & Johnson, Miami Lakes, FL, USA) or a paclitaxel-eluting stent (PES; Taxus Express\™; Boston Scientific, Natick, MA, USA). From March 2010, second-generation DESs were available in Japan. The second-generation DESs used were an everolimus-eluting stent (EES; Xience; Abbott Vascular, Santa Clara, CA, USA; and Promus; Boston Scientific, Natick, MA, USA), a zotarolimus-eluting stent (ZES; Endeavor and Resolute; Medtronic Inc., Santa Rosa, CA, USA) and a biolimus-eluting stent (BES; Nobori®; Terumo, Tokyo, Japan). A rotablator was used when necessary. The use of intravascular ultrasound to confirm optimal stent expansion was encouraged. Dual antiplatelet therapy (aspirin [162 mg/day] and ticlopidine [200 mg/day] or clopidogrel [75 mg/day]) was recommended for at least 2 weeks prior to PCI after assessing each patient’s tolerance to those drugs, and patients were followed up for at least 12 months after DES implantation.

The primary endpoint was the incidence of ISR at follow-up, defined as a stent stenosis > 50% in diameter anywhere within the stent and/or within the 5-mm borders proximal or distal to the stent. The secondary endpoints included the clinical follow-up data of major adverse cardiac events (MACEs) after PCI, with MACEs defined as cardiac death, nonfatal myocardial infarction, target lesion revascularization (TLR), and stent thrombosis. Clinical follow-up data were obtained from hospital charts and telephone interviews with the patients at one year after PCI. The diagnosis of myocardial infarction was based on ST-segment changes in at least two contiguous ECG leads and creatine kinase elevation to more than twice in the normal range. Cases with stent thrombosis were judged as definite or probable according to
the definitions of Academic Research Consortium\(^9\)). TLR was defined as revascularization not only inside the stent but also within the 5-mm borders proximal or distal to the stent segment of the initial procedure.

Quantitative coronary angiography (QCA) was performed before and after PCI and at follow-up. Lesion complexity was classified according to the American Heart Association/American College of Cardiology lesion type classification\(^1\(^0\)). The angiographic measurements included proximal and distal reference diameters, the minimum lumen diameter and lesion length. Late lumen loss was defined as the difference in the minimal lumen diameter immediately after PCI and on follow-up angiography. QCA was performed using the computer-assisted automated edge detection method (QAngio XA, version 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) at Kansai Medical University. All the angiographic data were obtained by two experienced interventional cardiologists blinded to the patient data.

**Statistical analyses**

Continuous variables were expressed as the mean ± standard deviation (SD) and compared using Student's unpaired \(t\)-test. Categorical variables were expressed as counts and percentages, and the chi-squared test or Fisher exact tests was used for comparisons. Logistic regression analysis models were used to assess the univariate and multivariable covariates associated with ISR. Specifically, all variables significantly associated with ISR on a univariate analysis (\(P < 0.05\)) were entered into a logistic multivariable model in order to determine independent predictors. The results of a logistic multivariable model were reported as the hazard ratios with 95% confidence intervals and \(P\) values. Differences were considered significant at \(P < 0.05\). All statistical analyses of recorded data were performed using the Excel statistical software package (Ekuseru-Toukei 2012; Social Survey Research Information Co., Ltd., Tokyo, Japan).

**Results**

We analyzed 194 consecutive HD patients (331 lesions) who underwent follow-up angiography after DES implantation. ISR was observed in 59 patients (30.4%) / 74 lesions (22.4%). The clinical characteristics of the HD patients with and without ISR are summarized in Table 1. There were no significant differences in the characteristics between these two groups.
| Characteristics       | ISR (-) (n = 135) | ISR (+) (n = 59) | P value |
|----------------------|-------------------|------------------|---------|
| Age (years)          | 65 ± 11           | 66 ± 7           | 0.95    |
| Sex (% male)         | 67                | 78               | 0.71    |
| BMI (kg/m$^2$)       | 22.9 ± 3.5        | 23.1 ± 3.3       | 0.60    |
| Risk factors         | 39                | 49               | 0.47    |
| Smoking (%)          | 53                | 66               | 0.29    |
| Diabetes mellitus (%)| 93                | 95               | 0.58    |
| Hypertension (%)     | 65                | 75               | 0.35    |
| Hyperlipidemia (%)   | 5.7 ± 6.6         | 5.4 ± 4.5        | 0.41    |
| Duration of HD (years)| 61       | 51               | 0.38    |
| Diagnosis            | 13                | 20               | 0.72    |
| Stable angina (%)    | 26                | 29               | 0.84    |
| ACS (%)              | 50                | 48               | 0.83    |
| OMI (%)              | 4                 | 3                | 0.96    |
| Previous PCI (%)     | 97                | 96               | 0.88    |
| Previous CABG (%)    | 4                 | 2                | 0.93    |
| Medication at procedure | 93         | 93               | 0.88    |
| Aspirin (%)          | 1                 | 5                | 0.87    |
| Ticlopidine (%)      | 12                | 14               | 0.93    |
| Clopidogrel (%)      | 50                | 56               | 0.67    |
| Cilostazol (%)       | 50                | 49               | 0.97    |
| ACE (%)              | 57.0 ± 14.8       | 57.7 ± 14.0      | 0.95    |
| ARB (%)              | 11.1 ± 1.5        | 11.1 ± 1.4       | 0.83    |
| β-blocker (%)        |                   |                  |         |
| Statin (%)           |                   |                  |         |
| Ejection fraction (%)|                   |                  |         |
| Hemoglobin (g/dl)    |                   |                  |         |
The lesion and procedural characteristics are shown in Table 2. The relative incidence of AHA/ACC type C lesion was increased in lesions with ISR compared to those without ISR. While no significant differences were noted in the rate of lesions with severe and moderate calcification between the two groups, the rate of rotational atherectomy use was higher in lesions with ISR than those without ISR (50% vs. 25%; P < 0.01). The stents were longer in the lesions with ISR than those without ISR (31.6 ± 16.9 vs. 25.8 ± 11.8 mm; P = 0.016).
| Characteristics                        | ISR (-) (n = 257) | ISR (+) (n = 74) | P value |
|---------------------------------------|-------------------|-----------------|---------|
| **Target vessels**                    |                   |                 |         |
| Left main (%)                         | 34                | 30              | 0.77    |
| Left anterior descending (%)          | 23                | 27              | 0.81    |
| Left circumflex artery (%)            | 33                | 40              | 0.49    |
| Right coronary artery (%)             | 12                | 0               | 0.007   |
| **ACC/AHA classification**            |                   |                 |         |
| A (%)                                 | 11                | 14              | 0.77    |
| B1 (%)                                | 56                | 41              | 0.29    |
| B2 (%)                                | 33                | 45              | 0.17    |
| C (%)                                 | 25                | 34              | 0.11    |
| **Lesion type**                       |                   |                 |         |
| Discrete (%)                          | 40                | 53              | 0.15    |
| Tubular (%)                           | 4                 | 3               | 0.54    |
| Diffuse (%)                           | 0.4               | 0               | 0.78    |
| **Angiographic calcification**        |                   |                 |         |
| Moderate (%)                          | 37                | 50              | 0.15    |
| Severe (%)                            | 18                | 23              | 0.12    |
| Eccentric lesion (%)                  | 11                | 14              | 0.53    |
| **Thrombus (%)**                      |                   |                 |         |
| Thrombus (%)                          | 25                | 23              | 0.94    |
| **Dissection (%)**                    |                   |                 |         |
| Dissection (%)                        | 20                | 19              | 0.99    |
| **Haziness (%)**                      |                   |                 |         |
| Haziness (%)                          | 25                | 50              | 0.0003  |
| **Irregular lesion surface (%)**      | 2.98 ± 0.40       | 3.0 ± 0.41      | 0.97    |
| **Ostial lesion (%)**                 | 25.8 ± 11.8       | 31.6 ± 16.9     | 0.016   |
| **In stent restenosis (%)**           |                   |                 |         |
| Characteristics                              | ISR (-) (n = 257) | ISR (+) (n = 74) | P value |
|---------------------------------------------|-------------------|------------------|---------|
| Chronic total occlusion (%)                 |                   |                  |         |
| Bifurcation (%)                             |                   |                  |         |
| Final kissing balloon technique (%)         |                   |                  |         |
| Rotational atherectomy (%)                  |                   |                  |         |
| Stent size (mm)                             |                   |                  |         |
| Total stent length (mm)                     |                   |                  |         |

HD: hemodialysis, ISR: in-stent restenosis

The QCA measurements of the lesions were shown in Table 3. The minimal lumen diameter before DES implantation was smaller (0.82 ± 0.49 vs. 0.97 ± 0.45 mm; P < 0.01) and the lesion length was longer (30.2 ± 16.1 vs. 24.4 ± 12.1 mm; P = 0.023) in the lesions with ISR than those without ISR. On a univariate analysis, the incidence of ISR was associated with AHA/ACC type C lesions (P = 0.013), rotational atherectomy use (P < 0.001), lesion length (P = 0.003) and the minimal lumen diameter before DES implantation (P = 0.011). On a multivariate analysis, rotational atherectomy use (odds ratio [OR]: 2.71, 95% confidence interval [CI] 1.55–4.72, P < 0.001), lesion length (OR: 1.02, 95% CI 1.01–1.04, P = 0.030) and the minimal lumen diameter before DES implantation (OR: 0.50, 95% CI 0.27–0.91, P = 0.034) were independent risk factors for ISR after DES implantation in HD patients (Table 4).
Table 3
Quantitative coronary Angiographic analysis

| Characteristics | ISR (-) (n = 257) | ISR (+) (n = 74) | P value |
|-----------------|-------------------|------------------|---------|
| Reference Diameter | 2.46 ± 0.60 | 2.38 ± 0.59 | 0.36 |
| Pre-procedure (mm) | 2.79 ± 0.53 | 2.70 ± 0.52 | 0.24 |
| Follow-up (mm) | 0.97 ± 0.45 | 0.82 ± 0.49 | 0.009 |
| Minimal lumen Diameter | 2.46 ± 0.55 | 2.41 ± 0.59 | 0.22 |
| Pre-procedure (mm) | 2.24 ± 0.53 | 0.89 ± 0.53 | < 0.001 |
| Post-procedure (mm) | 24.4 ± 12.1 | 30.2 ± 16.1 | < 0.001 |
| Follow-up (mm) | 0.22 ± 0.45 | 1.52 ± 0.71 | < 0.001 |
| Lesion length (mm) | | | |
| Late loss (mm) | | | |

HD: hemodialysis, ISR: in-stent restenosis

Table 4
Predictors for ISR

| Predictor | Univariate analysis | Multivariate analysis |
|-----------|---------------------|-----------------------|
|           | odds | 95%CI | P value | odds | 95%CI | P value |
| AHA/ACC type C lesion | 1.95 | 1.15–3.30 | 0.013 | 2.71 | 1.55–4.72 | < 0.001 |
| rotational atherectomy use | 2.95 | 1.73–5.05 | < 0.001 | 1.02 | 1.00–1.04 | 0.030 |
| Lesion length | 1.03 | 1.01–1.05 | 0.003 | 0.50 | 0.27–0.91 | 0.024 |
| MLD before procedure | 0.47 | 0.27–0.84 | 0.011 | | | |

MLD; minimal lumen diameter

The MACEs at one year are shown in Table 5. MACEs were observed in 59 patients (30.4%). Cardiac death was observed in 2 patients (1.0%), nonfatal myocardial infarction in 8 patients (4.1%), target lesion revascularization in 59 patients (30.4%), and stent thrombosis in 2 patients (1.0%). All patients continued to take their medication without skipping doses.
Table 5
MACEs at 1 year

|                        |       |
|------------------------|-------|
| Number of patients     | 194   |
| Major adverse cardiac events | 59 (30.4%) |
| Cardiac death          | 2 (1.0%) |
| Nonfatal myocardial infarction | 8 (4.1%) |
| Target lesion revascularization | 58 (29.9%) |
| Stent thrombosis       | 2 (1.0%) |

The first-generation DESs were implanted in 120 lesions, and the second-generation DESs were implanted in 211 lesions. The number of lesions treated with each DES type and the ISR rate are shown in Table 6. The incidence of ISR was similar between the lesions treated with the first-generation DESs (25.8%) and the second-generation DESs (20.4%) (P = 0.25). The rate of ISR was 28.9% for SESs, 13.1% for PESs, 19.4% for EESs, 15.8% for ZESs, and 30.0% for BESs. There was no significant difference in the ISR rate among different DES types.

Table 6
The number of lesions and ISR rate stratified by DES types

| DES type          | Number of lesions | ISR (%) |
|-------------------|-------------------|---------|
| First-generation DES | 120              | 25.8    |
| SES               | 97                | 28.9    |
| PES               | 23                | 13.1    |
| Second-generation DES | 211              | 20.4    |
| EES               | 142               | 19.4    |
| ZES               | 38                | 15.8    |
| BES               | 30                | 30.0    |

DES: drug eluting stent SES: sirolimus-eluting stent PES: paclitaxel-eluting stent EES: everolimus-eluting stent ZES: zotarolimus-eluting stent BES: biolimus-eluting stents

Discussion

In the present study, we showed that the incidence of ISR after DES implantation in HD patients was 22.4%. Furthermore, a small minimal lumen diameter before DES implantation, a longer lesion length before DES implantation and the use of rotational atherectomy were independent predictors of ISR after DES implantation in patients on HD. PCI is widely performed in HD patients with coronary artery disease\(^4,11\). In addition, current guidelines recommend the use of DESs in HD patients\(^7\). Since previous
studies reported the ISR rate in HD patients in relatively small number of lesions\textsuperscript{12–20}, our present study represents an important contribution to the literature on the angiographic outcomes of PCI in HD patients.

Compared with previous studies in non-HD patients\textsuperscript{8}, we found that the incidence of ISR and MACEs was high in HD patients. In previous reports on ISR rate in HD patients\textsuperscript{12–20}, the incidence of ISR was 21.2%-39.5% for SES, 13.6% for PES, and 8.7%-16.0% for EES\textsuperscript{12–20}. In the present study, the incidence of ISR for all DESs was 22.4%, which was slightly higher than that reported in previous reports. Although the reasons for the higher rate of restenosis in this study are not clear, the relatively frequent use of rotational atherectomy (31%) and longer lesion length (25.6 ± 13.3 mm) may be involved.

Although this study was not designed to elucidate the mechanisms underlying the high rate of ISR in HD patients, we propose several possible explanations. First, stents in severely calcified lesions are frequently underexpanded and malapposed, which are well-known risk factors for ISR\textsuperscript{21}. Second, calcification and vascular stiffness may cause stent edge dissections and increase the degree of vascular injury, thereby predisposing the lesions to restenosis\textsuperscript{22}. Third, both the number and function of endothelial progenitor cells (EPCs) are reduced in patients with chronic renal failure compared with healthy patients\textsuperscript{23,24}. Furthermore, HD patients tend to have traditional risk factors for coronary arteriosclerosis, such as diabetes and hyperlipidemia. These risk factors also deplete the circulating EPCs and inhibit their functions\textsuperscript{23,25,26}. Because EPCs play a key role in the maintenance of vascular integrity and act as repair cells in response to endothelial injury, reduced number and function of EPCs in HD patients may contribute to higher rate of ISR. Fourth, the activation of the coagulation system, increased platelet aggregability, and the release of oxidant free radicals during dialysis sessions may contribute to the growth of neointimal hyperplasia\textsuperscript{27}.

Predictors for ISR in HD patients at follow-up in this study were a small minimal lumen diameter before DES implantation, a longer lesion length before DES implantation, and the use of rotational atherectomy. These predictors of ISR differ from those in patients with normal renal function. Indeed, the typical risk factors such as diabetes, hypertension, small vessel size, or AHA/ACC type B2/C lesions showed no significant correlation with ISR in this study. A previous study reported that coronary calcification and the use of rotational atherectomy, but not a small minimal lumen diameter or long lesion length before DES implantation, were predictors of target-vessel revascularization\textsuperscript{19}.

The second-generation DESs may be associated with a reduced incidence of ISR compared with the first-generation DESs, as the second-generation DESs have newer polymer coatings and thinner struts. However, in previous studies\textsuperscript{28,29,30}, the incidence of ISR was not significantly different between the first- and the second-generation DESs in non-HD patients. Consistent with those studies, we found that the incidence of ISR was similar between lesions treated with the first-generation DESs (25.8%) and the second-generation DESs (20.4%) in HD patients. Although different types of stents were used in different numbers of lesion in this study, the incidence of ISR was comparable among different stents. Future studies with larger number of lesions will be needed to define the incidence of ISR in different stent types.
Study limitations

Several limitations associated with the present study warrant mention. First, the study was limited by its small sample size, its retrospective nature, and its nonrandomized fashion. Second, all patients were Japanese. A previous study reported that Japanese patients have a better prognosis than subjects in other countries\(^3\). This racial prognostic difference should be considered when interpreting our results. Third, this study analyzed lesions with QCA but not with intravascular ultrasound. Although intravascular ultrasound was performed in all patients in this study, the measurements and the actual cross-sectional area obtained on intravascular ultrasound were not considered.

Conclusions

In conclusion, DES implantation in HD patients is associated with a high incidence of ISR (22.4%) at follow-up. A small MLD, long LL and the use of rotational atherectomy were independent predictors of ISR after DES implantation in patients on HD. Furthermore, the use of the second-generation DESs was not associated with a reduced incidence of ISR in this study. Further studies in larger populations will be necessary to clarify whether the second-generation DESs in general or certain stent types of the second-generation DESs in particular offer tangible benefits in HD patients.

Abbreviations

**HD**: hemodialysis

**PCI**: percutaneous coronary intervention

**DES**: drug-eluting stent

**ISR**: in-stent restenosis

**SES**: sirolimus-eluting stent

**PES**: paclitaxel-eluting stent

**EES**: everolimus-eluting stent

**ZES**: zotarolimus-eluting stent

**BES**: biolimus-eluting stent

**MACEs**: major adverse cardiac events

**TLR**: target lesion revascularization

**QCA**: Quantitative coronary angiography
Availability of Data and Materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Kansai Medical University Ethics Committee Review Board and written informed consent was waived because of the retrospective and observational study design. The study was registered before patient enrollment at Kansai Medical University.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Contributions

HS and MM did the initial idea for the study and making the protocol. HS, SM, MT and ST contributed on the acquiring data, data analysis and technical advice to research assistants. IS contributed important intellectual content during manuscript revision. All authors have checked and approved the final manuscript.

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