Impact of Insulin-Treated Diabetes and Hemodialysis on Long-Term Clinical Outcomes Following Sirolimus-Eluting Stent Deployment – Insights From a Sub-Study of The Cypher Stent Japan Post-Marketing Surveillance (Cypher J-PMS) Registry –

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Background: Long-term clinical outcomes of diabetes mellitus (DM) patients who underwent drug-eluting stent deployment has not well investigated.

Methods and Results: A total of 2,050 cases were enrolled consecutively from 50 sites in Japan into the Cypher stent Japan Post-Marketing Surveillance (Cypher J-PMS) registry, and the 3-year outcomes of DM patients were analyzed. Subjects were divided into 2 groups based on the treatment of DM (insulin-treated diabetics (IT) group, n=207; and non insulin-treated diabetes (NIT) group, n=682). Major adverse cardiac event (MACE) rates in the IT group and the NIT group were 26.0% and 14.5% at 3 years, respectively (P<0.001). There were no significant differences in stent thrombosis rates (definite and probable by Academic Research Consortium (ARC) definition) (0% and 1.08%, respectively). Multivariate analysis suggested that hemodialysis and insulin-treated DM were independent predictors for MACE, and insulin-treated DM, hemodialysis and long lesions were strong independent predictors for target-lesion revascularization (TLR).

Conclusions: Hemodialysis and insulin-treated DM were strong independent predictors of mortality and TLR in DM patients. These results might suggest that special attention to patients with hemodialysis and insulin-treated DM is warranted in the setting of sirolimus-eluting stent deployment for DM patients. (Circ J 2010; 74: 2592–2597)

Key Words: Angioplasty; Drug-eluting stent; Follow-up studies

The prevalence of diabetes mellitus (DM) has increased rapidly and significantly, posing an ever increasing major threat to human health. DM is a known risk factor of cardiovascular disease. Additionally, DM is an independent predictor of cardiovascular event in patients undergoing percutaneous coronary intervention (PCI). Despite advancements in PCI treatment methods, including the advent of stenting, DM remains a strong predictor of adverse events for patients undergoing PCI.

However, recent trials have demonstrated the clinical efficacy of drug-eluting stent (DES) in a variety of lesion morphology and clinical presentation such as DM and acute myocardial infarction (MI) compared to bare-metal stent (BMS). These findings have further promoted the widespread use of PCI for coronary revascularization. However, highly variable outcomes regarding mortality of DM patients have been reported among trials. In particular, their efficacy among insulin-treated DM patients has not been well studied, and long-term follow-up outcomes were limited to a relatively short period. Therefore, we investigated the long-term durability of DES for DM patients according to whether insulin treatment was part of their therapy. Thus, we report 3-year follow-up data from a post-marketing surveillance study of sirolimus-eluting stents (SES; Cypher stent, Cordis Corp, Johnson and Johnson Company, Warren, NJ, USA) in Japan. During enrollment into this registry, the only available DES in Japan was SES. Therefore, the true impact on a real-world practice can be seen very clearly.

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Methods
The Cypher stent Japan Post-Marketing Surveillance (Cypher J-PMS) is a post-marketing surveillance registry aimed at evaluating the safety and efficacy of SES in routine daily practice in the Japanese population. A total of 2,050 consecutive patients who underwent SES deployment were registered from September 2004 through September 2005 at 50 sites throughout Japan. The use of DES was left to each operator’s discretion (which included off-label use of the product). SES deployment was performed according to standard interventional techniques. The post procedural antiplatelet regimen consisted of lifelong aspirin (81–162 mg/day) and ticlopidine (200 mg/day for more than 3 months). Angiographic follow up was mandated at 8 months, and clinical follow up was scheduled every year up to 5 years.

The diagnosis of DM was based on the need for treatment with insulin or oral hypoglycemic drugs or a confirmed elevated blood glucose level. DM was present in 889 patients accounting for 43.3% of the overall population. DM patients were further divided into 2 groups based on the status of treatment (insulin-treated diabetes (IT) group: n=207, non-insulin-treated diabetes (NIT) group: n=682). Clinical efficacy and safety were compared among the 2 groups. This study was approved by the Institutional Review Boards of participating institutions.

Clinical Follow up
The primary end-point of this study was the composite outcome of a major adverse cardiac event (MACE) at 3 years. MACE was defined as death by any cause, non-fatal MI, emergent bypass surgery, and target-lesion revascularization (TLR) at 3 years. TLR was defined as coronary artery bypass grafting (CABG) or repeat PCI procedure at the original lesion site including the area inside the stent and the 5-mm vessel segments adjacent to it, and a target vessel-revascularization (TVR) as PCI or CABG of the treated vessel. Stent thrombosis was evaluated by the Academic Research Consortium (ARC) definition using the definite/confirmed and probable categories. Target-vessel failure (TVF) was defined as the composite of cardiac death, non-fatal MI, and target-vessel revascularization in the same epicardial vessel. Clinical outcome at 3 years was determined during outpatient clinic visits or by telephone interviews.

Statistical Analysis
Continuous variables were expressed as mean±standard deviation and categorical data were presented as frequencies. For comparisons between groups, Fisher’s exact test or an ANOVA test was used as appropriate. Both TLR and MACE rates during the follow-up period were analyzed by the Kaplan-Meier method. A log-rank test was used for survival comparisons. Multivariable Cox proportional hazards regression model with a step-wise selection process and an entry/exit criterion of 0.20 was used to examine the predictors and adjusted hazard ratios for MACE and TLR. A P value <0.05 was considered statistically significant.

Results
Patient Demographics
Patient demographics are shown in Table 1. The IT group
was significantly younger than the NIT group. Although there was no difference in the proportion of patients who had a history of coronary artery revascularization, multi-vessel disease was more frequently observed in the IT group. Furthermore, patients with low left ventricle ejection fraction (LVEF) and hemodialysis patients were more frequently observed in the IT group.

### Lesion Characteristics
Lesion characteristics are shown in Table 2. There were no significant differences in the proportions of lesion morphology types according to the AHA/ACC classification. Furthermore, there was no significant difference in the frequency of lesion morphology such as severe calcification, bifurcation and ostial lesion.
Index Procedure

Intravascular ultrasound (IVUS) was frequently used (approximately 70% of cases) at the time of PCI in both groups. There were no significant differences in the number of stents deployed per lesion and in the maximum stent deployment pressures (Table 2). The complete revascularization rate was 25% in both groups.

Clinical Follow-up

A 3-year clinical follow up was available for 95.3% of patients. The median duration of follow up was 1,121 days (95-percentile: 368–1231 days), and there was no significant difference between the 2 groups (IT group: 1,051 days; NIT group: 1,070 days; P=0.263). The number of patients receiving dual antiplatelet therapy at 1,440 days was 35.7% in the IT group and 40.4% in the NIT group. Clinical outcomes are listed in Table 3. The MACE rates in the IT group and the NIT group were 26.0% and 14.5%, respectively (P<0.001). Differences in MACE rates were mainly driven by differences in TLR and death rates. There was no difference in non-target-lesion TVR, and the rates of stent thrombosis in the IT group and the NIT group were 0.00% and 1.08%, respectively (P=0.208). Figure shows the Cardiac death + MI-, TLR-, and TVF-free survival curves for the 2 groups.
It has also been shown that DM remains a significant risk factor of TLR in DM patients. Although these findings suggest that SES deployment for DM patients is safe, they call for special attention in DM patients who require both insulin-treatment and hemodialysis. Special attention in DM patients who require both insulin-treatment and hemodialysis is mandatory. We confirmed the widespread use of DES for off-label indications including in-stent restenosis, bifurcation lesion, and chronic total occlusion. More than 80% of cases in this analysis were off-label usage of DES representing a real world practice. In the present study, the 3-year MACE rate was 26% in the IT group and 14.5% in the NIT group. Multivariate analysis revealed that insulin-treated DM was a significant independent predictor of both MACE and TLR. These findings might clearly demonstrate the differences in DES efficacy within DM patients and seems to be consistent with recently published data. In the NHLBI registry, the overall beneficial effect of DES in reducing TLR was demonstrated in both insulin-treated and non-insulin treated DM patients, as compared to BMS. However, no differences in death and MI risk was noted between DES and BMS in insulin-treated DM patients.15 Ortolani et al demonstrated that the use of DES for DM patients was associated with a reduced 2-year MACE rate compared to BMS. However, this beneficial effect was limited to non-insulin dependent DM patients.15 In the IT group, MACE mainly contributed to the death rate and TLR. The complete revascularization rate might affect long-term outcomes, however, there was no difference between both groups in this sub-study. Although the IT group was younger than the NIT group, it was associated with morbidities such as low LVEF, multi-vessel disease, and hemodialysis more frequently than the NIT group. These differences in clinical demographics are likely to explain the worthy prognosis in the IT group.

Another important point of this study was that the efficacy of SES was significantly attenuated in the IT group compared to the NIT group. There was no difference in angiographic features including vessel size, lesion length, and lesion morphology between the 2 groups, and multivariate analysis showed that insulin-treated DM and hemodialysis were independent predictors for TLR. These findings might suggest that pathophysiological aspects such as renal dysfunction and insulin-treated DM might highly affect the efficacy of SES. Another explanation is that vessel calcification associated with these circumstances contributed to stent malapposition and insufficient drug delivery. However, it is difficult to pinpoint an exact explanation and further investigation is warranted to assess the attenuated efficacy of SES in insulin-treated DM patients. Surprisingly, there was no difference with respect to the rate of non-target-lesion TVR. A clear explanation of this finding is difficult and further investigation seems to be required. However, these findings might support the poor long-term outcomes in DM patients after DES treatment16 and also support the recent investigation that failed to demonstrate the beneficial effect of PCI followed by optimal medical treatment compared to optimal medical treatment.17 The combination of optimal PCI and optimal medical treatment might be the next step to overcome the inferiority of long-term outcomes in DM patients.

### Safety of SES in Diabetic Patients

Concerns related to DES stent thrombosis have emerged. In this analysis, stent thrombosis was approximately 1% at 3 years and there was no difference in the incidence of stent thrombosis between the 2 groups. Furthermore, the use of dual antiplatelet therapy was limited to approximately 40% in our cohort. These findings suggest the safety of DES. In a previous report, DM was reported to be an independent predictor for stent thrombosis.19 Iakovou et al reported that DM...
had a risk of stent thrombosis with a hazard ratio of 5.96. Furthermore, a relatively lower safety risk for off-label use was reported. Therefore, our findings are inconsistent with the aforementioned reports. The reason for the discrepancy of the findings remains unknown. A possible explanation could be the difference in ethnicity, the technical treatment strategy, as evidenced by the high rate of IVUS use during PCI in this study (72.2%), and clinical indication. Park et al. mentioned that DM was not associated with an excess risk of stent thrombosis. These data might suggest the difference in ethnicity. Further study is warranted to confirm the safety of DES for DM patients in a real-world practice.

Study Limitations
This subset study has several important limitations. First, this is a non-randomized observational study. Second, we could not correctly examine the influence of glycemic control on rates of restenosis and revascularization. It has been known that angiographic follow up might influence revascularization rates because of angiographically driven revascularization, especially in patients with diabetes and hemodialysis. Therefore, the present study that mandated angiographic follow up might underestimate the clinical significance of SES. Finally, because there are no comparative data available, we could not confirm the impact of ethnicity on our results.

Conclusions
DM patients who were treated with insulin were associated with higher mortality and required more frequent TLR, and also TVF; however, there were no significant differences in the incidence of stent thrombosis at 3 years. Hemodialysis and insulin-treated DM were strong independent predictors of mortality when SES was used, and also of TLR in DM patients. Special attention to patients treated with hemodialysis and insulin treatment warranted in the setting of SES deployment though this sub-study suggests the safety of SES deployment for DM patients.

Disclosure
All authors stated no conflict of interest.

References