Three-Year Clinical Outcomes of Everolimus-Eluting Stents From the Post-Marketing Surveillance Study of Cobalt-Chromium Everolimus-Eluting Stent (XIENCE V/PROMUS) in Japan

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**Background:** The Cobalt-Chromium Everolimus-Eluting Stent (CoCr-EES) Post-marketing Surveillance (PMS) is a prospective multicenter registry designed to evaluate the safety and efficacy of XIENCE V/PROMUS everolimus-eluting stents in routine clinical practice at 47 centers representative of the clinical environment in Japan.

**Methods and Results:** We enrolled 2,010 consecutive patients (2,649 lesions) who underwent PCI using CoCr-EES. Clinical outcomes were evaluated for up to 3 years. Clinical follow-up was available in 1,930 patients (96%) at 3 years. Major adverse cardiovascular events (MACE) occurred in 6.8% of patients, including cardiac death (1.7%), myocardial infarction (1.5%), and clinically driven target lesion revascularization (CD-TLR, 4.2%). Late CD-TLR rate was 0.8% from 1 to 2 years, and 0.5% from 2 to 3 years. Definite or probable stent thrombosis occurred in 7 patients (0.3%) up to 1 year. There was no very late definite or probable stent thrombosis from 1 to 3 years. Significant independent predictors for MACE were hemodialysis, prior coronary intervention, triple-vessel coronary artery disease, and age >70 years.

**Conclusions:** Three-year clinical outcomes from the CoCr-EES PMS demonstrated a low incidence of clinical events. There was no major concern about very late stent thrombosis or late catch-up phenomenon in patients treated with EES in routine clinical practice in Japan. (*Circ J* 2016; 80: 906–912)

**Key Words:** Everolimus; Restenosis; Stent; Thrombosis

Late stent thrombosis and late in-stent restenosis are the 2 major limitations of first-generation drug-eluting stents (DES). Second-generation DES are associated with significantly lower in-stent restenosis rate and lower rate of late stent thrombosis as compared with first-generation DES. Therefore, second-generation DES are used currently as the first-line coronary stent in routine clinical practice. Clinical outcomes of first-generation DES, such as sirolimus- and paclitaxel-eluting stents, in earlier Japanese post-marketing surveillance studies (PMS) have been published previously, but long-term clinical outcomes for second-generation DES, such as cobalt-chromium everolimus-eluting stents (CoCr-EES), have not been fully evaluated in routine clinical practice in Japan. Therefore, we evaluated 3-year clinical outcomes after EES implantations in a real-world setting at 47 Japanese sites using the EES Japan PMS database.

**Methods**

**Subjects and Follow-up**

CoCr-EES PMS Japan is a prospective multicenter registry enrolling 2,000 patients who received CoCr-EES. The study was designed to evaluate the safety and efficacy of the CoCr-EES in routine clinical practice shortly after the launch of...
CoCr-EES in Daily Clinical Practice in Japan. A total of 47 centers across Japan participated in the PMS. Patients were eligible for the study if ≥1 native coronary artery lesions were treated exclusively with CoCr-EES (XIENCE V or PROMUS) during the index percutaneous coronary intervention (PCI) procedure and written informed consent was obtained. We excluded those patients who were treated with stents other than CoCr-EES, or underwent concomitant treatment of a graft vessel. Patients were invited to enroll in the study after apparently successful PCI. The relevant review boards in all participating centers approved the study protocol.

Pre-procedural patient preparations were performed according to the health-care facility’s standard of care for interventional cardiology, and the treatment strategy was left to the discretion of the attending physicians and PCI operators. The sizes of CoCr-EES available for use were: 2.5, 2.75, 3.0 and 3.5 mm in diameter, and 8, 12, 15, 18, 23 and 28 mm in length. Use of multiple overlapping of stents was allowed, if necessary. Clinical data were collected and documented in an electronic case report form (Medidata, NY, USA) at the following time points: baseline, after the procedure, 8 months, 1 year, 2 years, and 3 years. Pre-specified clinical events such as death,
definitions of coronary risk factors were decided in each participating hospital. All deaths were considered as cardiac death unless an unequivocal non-cardiac cause was established. Specifically, any unexpected death, even in patients with coexisting potentially fatal non-cardiac disease (eg, cancer, infection), was classified as a cardiac death. MI was defined as development of new, pathological Q waves on electrocardiogram, or elevation of creatinine kinase (CK) ≥2-fold the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves. Target lesion revascularization (TLR) was defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR was classified prospectively as clinically indicated or non-clinically indicated by the physician prior to repeat angiography. The target lesion was defined as the treated segment from 5 mm proximal to the stent to 5 mm distal to the stent. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass for any segment in the target vessel. Major adverse cardiac events (MACE) were defined as the composite of cardiac death, MI, and clinically driven TLR. Target lesion failure (TLF) and target vessel failure (TVF) were defined as the composite of cardiac death, target vessel MI, clinically driven TLR, and the composite of cardiac death, MI, and TVR, respectively. Stent thrombosis was defined as definite, probable, and possible according to the ARC definition. Revascularization was considered clinically indicated if: (1) in addition to an angiographic minimum lumen % diameter stenosis (DS) ≥50% on core laboratory QCA, the patient also presented with one of the following: positive history of recurrent angina pectoris, presumably related to the target vessel; objective signs of ischemia at rest or during exercise test, presumably related to the target vessel; abnormal results of any invasive functional diagnostic test; or (2) TLR or TVR was performed for a lesion with %DS ≥70% on core laboratory QCA even in the absence of the aforementioned ischemic signs or symptoms.

**Definitions**

In this registry, definitions of coronary risk factors were decided in each participating hospital. All deaths were considered as cardiac death unless an unequivocal non-cardiac cause was established. Specifically, any unexpected death, even in patients with coexisting potentially fatal non-cardiac disease (eg, cancer, infection), was classified as a cardiac death. MI was defined as development of new, pathological Q waves on electrocardiogram, or elevation of creatinine kinase (CK) ≥2-fold the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves. Target lesion revascularization (TLR) was defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR was classified prospectively as clinically indicated or non-clinically indicated by the physician prior to repeat angiography. The target lesion was defined as the treated segment from 5 mm proximal to the stent to 5 mm distal to the stent. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass for any segment in the target vessel. Major adverse cardiac events (MACE) were defined as the composite of cardiac death, MI, and clinically driven TLR. Target lesion failure (TLF) and target vessel failure (TVF) were defined as the composite of cardiac death, target vessel MI, clinically driven TLR, and the composite of cardiac death, MI, and TVR, respectively. Stent thrombosis was defined as definite, probable, and possible according to the ARC definition. Revascularization was considered clinically indicated if: (1) in addition to an angiographic minimum lumen % diameter stenosis (DS) ≥50% on core laboratory QCA, the patient also presented with one of the following: positive history of recurrent angina pectoris, presumably related to the target vessel; objective signs of ischemia at rest or during exercise test, presumably related to the target vessel; abnormal results of any invasive functional diagnostic test; or (2) TLR or TVR was performed for a lesion with %DS ≥70% on core laboratory QCA even in the absence of the aforementioned ischemic signs or symptoms.

**Statistical Analysis**

Statistical analysis was performed using SAS (version 9.3; SAS Institute; Cary, NC, USA). For binary variables, counts, percentages, and 95% CI were calculated. Pearson chi-squared test or Fisher’s exact test was performed when appropriate. For continuous variables, mean±SD, and 95% CI for the mean were calculated. Cumulative event curves were estimated according to the Kaplan-Meier method. Finally, predictors for MACE were identified using multivariate stepwise cox regression, in which variables were entered into the model at the 0.2 significance level and removed at the 0.05 level (from the Wald chi-square statistic). Variables were eligible for inclusion in the multivariate regression model if the variable was available in ≥90% of the subjects, and had a univariate P<0.2 (Table S1). If a given variable was highly correlated with other variables (r>0.5 and P<0.05), we selected the variable with the highest level of significance. Candidate predictors are listed in Tables 1–3. Two-tailed P<0.05 was considered significant.
Patient, lesion and procedural characteristics were typical of the PMS of DES in Japan (Tables 1, 2). The average age was 68.8±10.1 years. The prevalence of diabetes was 41.9% and dialysis was 4.9%. Average reference vessel diameter was 2.57±1.36 mm, and lesion length was 17.8±12.0 mm. Prevalence of type B2/C lesion was 81.9%. An average of 1.3±0.6 lesions were treated with an average of 1.2±0.5 stents per lesion.

At 8 months, serial QCA was available in 1,848 lesions.

### Results

From March 2010 to June 2011, a total of 2,033 patients were consecutively enrolled at 47 sites in Japan (Table S2). We excluded 23 patients due to non-study stent implantation (n=10), study stent implantation only within a bypass graft (n=4), withdrawal of consent (n=4), or repeated enrollment (n=5). Thus, a total 2,010 patients (2,649 lesions) constituted the subject group (Figure 1).
Three-year clinical follow up was available for 1,930 patients (96%). Dual antiplatelet therapy (DAPT) was continued in 84.6% of patients at 1 year, in 71.5% at 2 years and in 64.0% at 3 years. At 3 years, MACE occurred in 137 patients (6.8%; Table 4). Cumulative incidences of MACE and of clinically driven TLR were 7.1% and 4.4% at 3 years, respectively (Figure 2). Late clinically driven TLR rate in the complex lesion subsets was 4.3% in the bifurcation lesions, 7.6% in the chronic total occlusive lesions, 7.1% in in-stent restenosis lesions, 9.9% in the ostial lesions, 5.6% in the overlap stenting lesions, and 6.5% in the moderate or severe calcified lesions, respectively. Incidence of definite or probable stent thrombosis was 0.3% at 1 year without any further increase beyond 1 year and up to 3 years (Table 4). Within 3 years, 6 definite and 1 probable stent thrombosis occurred (Table 5). Significant independent multivariate predictors of MACE were hemodialysis, prior coronary intervention, 3-vessel disease, and age ≥70 years (Table 6).

**Discussion**

The major findings of the present study were: (1) CoCr-EES is safe and effective at 3 years in routine daily practice in this multicenter PMS in Japan; (2) binary restenosis rate was low with small late loss at 8 months, and this neointimal suppression was maintained up to 3 years; (3) very late definite or probable stent thrombosis was not observed beyond 1 year; (4) there was no concern about late catch-up phenomenon and late stent thrombosis following CoCr-EES implantation, even in this real world setting; and (5) hemodialysis was the strongest independent predictor of MACE.

**Table 5.** Definite or Probable Stent Thrombosis Patient Characteristics

<table>
<thead>
<tr>
<th>Stent thrombosis</th>
<th>Patient ID no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Days</td>
<td></td>
<td>35</td>
<td>1</td>
<td>6</td>
<td>68</td>
<td>1</td>
<td>188</td>
<td>9</td>
</tr>
<tr>
<td>DAPT</td>
<td></td>
<td>On</td>
<td>On</td>
<td>On</td>
<td>On</td>
<td>On</td>
<td>On</td>
<td>On</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>64</td>
<td>74</td>
<td>79</td>
<td>66</td>
<td>68</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Clinical presentation†</td>
<td></td>
<td>UAP</td>
<td>STEMI</td>
<td>STEMI</td>
<td>Silent ischemia</td>
<td>UAP</td>
<td>Silent ischemia</td>
<td>UAP</td>
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<tr>
<td>Treated vessel†</td>
<td></td>
<td>RCA</td>
<td>NA</td>
<td>NA</td>
<td>RCA</td>
<td>RCA</td>
<td>RCA</td>
<td>LAD</td>
</tr>
<tr>
<td>Calcification†</td>
<td></td>
<td>Moderate</td>
<td>NA</td>
<td>NA</td>
<td>Severe</td>
<td>None/Mild</td>
<td>Severe</td>
<td>None/Mild</td>
</tr>
<tr>
<td>Bifurcation†</td>
<td></td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>In-stent restenosis†</td>
<td></td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic total occlusion†</td>
<td></td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>In-stent post %DS (%)†</td>
<td></td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
<td>9.11</td>
<td>9.9</td>
<td>28</td>
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<tr>
<td>Overlap stenting†</td>
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<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

†Analyzed by the independent core laboratory. DAPT, dual antiplatelet therapy; NA, not available; UAP, unstable anginapectoris. Other abbreviations as in Tables 1–3.

**Table 6.** Multivariate Predictors of 1,095-Day MACE

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis dependent</td>
<td>5.42</td>
<td>3.46–8.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>2.14</td>
<td>1.49–3.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>2.09</td>
<td>1.38–3.16</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>1.45</td>
<td>1.02–2.04</td>
<td>0.0406</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention. Other abbreviations as in Table 4.

(69.8%). In-stent late loss was 0.22±0.44 mm, and in-stent binary restenosis rate was 3.5% (Table 3).

The superiority of CoCr-EES compared with first-generation DES, other second-generation DES, and bare metal stents (BMS) has been reported in several meta-analyses.\(^3\)\(^–\)\(^6\),\(^11\),\(^12\) In particular, low stent thrombosis rates were reported in several clinical and lesion subsets. In the EXAMINATION trial, significantly lower stent thrombosis rate as compared with BMS was reported even in patients with ST-segment elevation MI, who are known to have the highest thrombotic risk.\(^13\),\(^14\) CoCr-EES was composed of a cobalt-chromium thin (81-μm) strut platform, thromboresistant 7.8-μm-thick fluororide and hexafluoropropylene polymer, and contained a low dose (1.0 μg/mm²) of everolimus. These characteristics all contribute to the high safety profile of CoCr-EES.

The present results were obtained in a PMS enrolling consecutive patients with successful CoCr-EES implantation and, therefore, are representative of actual routine clinical practice. Under these circumstances, the definite and probable stent thrombosis rate in this study was 0.3% at 3 years, which is similar to the rates reported in other regis-
tries and from randomized trials evaluating CoCr-EES.\textsuperscript{11,16–19} These results further confirmed the long-term safety of CoCr-EES. Furthermore, the long-term efficacy of EES was also confirmed in the present study. The late TLR rate following implantation of first-generation DES was reported to be approximately 2% per year in the previous Japanese studies.\textsuperscript{2,20} The precise mechanism of this phenomenon is unknown, but delayed healing, persistent inflammation, and in-stent neointimal growth might play important roles in delayed neointimal growth.\textsuperscript{21,22} In this study, late TLR rate beyond 1 year was 0.5–0.8%/year, which is less than half that observed with the first-generation DES. The more biocompatible polymer and the lower drug dose may have contributed to this favorable outcome.

**Predictors of MACE**

Diabetes mellitus is a well-known risk factor for early, late TLR, and MACE following sirolimus-eluting stent (SES) implantation.\textsuperscript{2,27,28} One possible mechanism contributing to this higher risk is the attenuation of the anti-proliferative effect of sirolimus under high glucose conditions.\textsuperscript{29} In the present univariate analysis, diabetes with treatment (oral drug or insulin) was one of the significant predictors for 3-year MACE (Table S1), but diabetes did not remain in the multivariate analysis, even though everolimus belongs to the limus family of drugs.\textsuperscript{30} For the subgroup analysis in the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET), the cumulative incidence of TLR in patients with insulin-treated diabetes mellitus was significantly lower in the SES group than in the SES group (9.2% vs. 16.1%; P=0.045).\textsuperscript{18} Further studies need to be carried out to determine whether this favorable effect in diabetic patients after EES implanted is a chance finding or not. Interestingly, this observation did not extend to dialysis. Dialysis is a well-known predictor for MACE after coronary stenting.\textsuperscript{2,28,25} Although only 4.9% of the patients were on dialysis, dialysis was the strongest predictor for MACE in the present study (Figure S1). Whereas clinically driven TLR rate was 2.5% at 1 year and 3.7% at 3 years in non-dialysis patients, it was 13.1% at 1 year and 18.4% at 3 years in dialysis patients. Similar results were also observed in the OUTFIT-PRO study, which noted a relatively high TVR rate following EES implantation (17% at 1 year) in dialysis patients.\textsuperscript{26} Thus, improved outcomes associated with EES use in non-dialysis patients cannot be generally extrapolated to dialysis patients. Although 1 randomized trial demonstrated superiority of EES compared with SES in dialysis patients,\textsuperscript{27} careful follow-up is warranted in hemodialysis patients with coronary artery disease treated with EES.

**DAPT**

Prolonged use of DAPT was associated with significantly lower incidence of stent thrombosis and MACE in the DAPT study, but it was also associated with a trend for increasing mortality.\textsuperscript{28,29} The prevalence of prolonged use of DAPT was high in this CoCr-EES PMS (71.5% at 2 years and 64.0% at 3 years) and no very late stent thrombosis was observed. Data on bleeding events, however, were not collected in the present study\textsuperscript{30} and, thus, untoward effects of this prolonged use of DAPT cannot be determined. The advantages and disadvantages of prolonged DAPT following EES could not be evaluated in this study. Further study is warranted to determine the optimal DAPT duration after EES implantation in routine daily practice.

**Study Limitations**

This study is a single-arm registry. Therefore, direct comparison with other therapies is not possible. The study sample size was not sufficient to evaluate the incidence of stent thrombosis, although the rate of stent thrombosis (very late stent thrombosis in particular), was remarkably low in the present study. Additionally, important data such as implanted stent diameter, stent length, use of coronary imaging (intravascular ultrasound and optical coherence tomography), and bleeding events were not obtained. This is the first large-scale multicenter study, however, to report long-term outcomes of second-generation EES based on routine clinical practice in Japan.

**Conclusions**

Three-year clinical outcomes of the XIENCE V/PROMUS PMS demonstrated a low incidence of clinical events in routine clinical practice in Japan. There were no major concerns about very late stent thrombosis or late catch-up phenomenon at up to 3 years.

**Acknowledgments**

The authors thank the members of the cardiac catheterization laboratory and clinical research coordinators at the participating centers. XIENCE V/PROMUS PMS was sponsored and funded by Abbott Vascular (ClinicalTrials.gov ID: NCT01086228).

**Disclosures**

K.K. and T.K. receive remuneration from Abbott Vascular; H.K. is an employee of Abbott Vascular and has stocks of Abbott Vascular; H.N. is an employee of Abbott Vascular; and T.K. receives research and scholar funds from Abbott Vascular. The other authors declare no conflicts of interest.

**References**


Supplementary Files

Supplementary File 1

Table S1. Univariate predictors of 1,095-day MACE

Table S2. Participating hospitals

Figure S1. Kaplan-Meier curves for 3-year major adverse cardiac events (MACE) vs. presence of hemodialysis.

Please find supplementary file(s):