Long-Term Clinical Outcome of Drug-Eluting vs. Bare-Metal Stent Implantation After Percutaneous Coronary Intervention in End-Stage Renal Disease Patients on Hemodialysis — Nationwide Cohort Study in Taiwan —

Mei-Ling Chen, MD; Jung-Lun Wu, MD; Michael Yu-Chih Chen, MD; Tsung-Cheng Hsieh, PhD

Background: Data on clinical outcome after drug-eluting stent (DES) vs. bare-metal stent (BMS) implantation in patients with end-stage renal disease (ESRD) under hemodialysis are limited and controversial.

Methods and Results: We identified 4,970 patients under chronic hemodialysis from Taiwan National Health Insurance Research Database (NHIRD) who had their first coronary stenting between 1 January 2007 and 31 December 2012. After 1:1 propensity score matching, we evaluated clinical outcomes for 1,151 patients in the DES group and 1,151 patients in the matched BMS group. We used ICD-9 CM codes or operation code to identify all outcomes in the study cohort after the index procedure. Primary outcomes including composite endpoints of mortality, non-fatal myocardial infarction (MI), non-fatal stroke, and revascularization after the index procedure were similar in both groups (HR, 0.94; 95% CI: 0.81–1.09; P=0.399). The results were consistent in various generations of DES vs. BMS groups. Secondary outcomes including mortality, non-fatal MI, non-fatal stroke, revascularization, cardiovascular death, hospitalization for heart failure, peptic ulcer bleeding or blood transfusion were similar in both groups, except for a lower risk of peptic ulcer disease in the DES group (HR, 0.59; 95% CI: 0.41–0.83; P=0.003) than the BMS group.

Conclusions: In patients on chronic hemodialysis, implantation of DES did not have a better clinical outcome than BMS.

Key Words: Bare-metal stent; Clinical outcome; Drug-eluting stent; End-stage renal disease; Hemodialysis
intervention procedures, and medical costs for >99% of the population in Taiwan. The diagnosis codes were based on the 9th revision of the International Classification of Diseases (ICD-9-CM). To ensure data privacy, individual identification was encrypted within the NHI database. This study was approved by the Research Ethics Committee of Hualien Tzu Chi Hospital (IRB number: IRB103-135-B).

Subjects
We enrolled adult patients with ESRD undergoing first PCI with stenting from 1 January 2007 to 31 December 2012. Date of index PCI was defined as the date on which the patients received the first implantation of DES or BMS. Patients were excluded if they met any of the following criteria: (1) confirmed cancer in the previous 5 years; or (2) received >1 type of stent on index procedure (i.e., both DES and BMS); or (3) aged <20 years old or >85 years old; or (4) received PCI with implantation of DES or BMS before a diagnosis of ESRD; or (5) length of hospital stay >30 days (Figure 1).

Propensity Score Matching
The 2 groups were enrolled via paired 1:1 matching for identical propensity score for gender, age, diabetes mellitus (DM) with insulin, DM without insulin, hyperlipidemia, hypertension, prior medication (aspirin, clopidogrel, proton pump inhibitors [PPI], β-blockers, angiotensin-converting enzyme inhibitor/aldosterone receptor blocker [ACEI/ARB], statins), prior history of stroke, myocardial infarction (MI), heart failure, and coronary artery bypass graft (CABG), and number of stents at first operation.

Definitions, Treatment and Endpoints
ESRD was identified on both ICD-9-CM codes and >3 months dialysis in the Registry for Catastrophic Illness Patient Database. The BMS group was identified according to PCI operation code (ICD-9: 36.06) with the medical device code for BMS. The DES group was identified using the by same operation code of PCI with the medical device code of DES, which was approved by the National Health Insurance Administration of Taiwan in December 2006. The present study enrolled patients with successful stent implantation because PCI procedure code and medical device code are used to claim reimbursement only in the situation of successful PCI and stent deployment. Baseline comorbidities were identified on ICD-9-CM codes diagnosed before the index procedure. The accuracy of the diagnoses of major diseases in the claims database has been further validated by relevant anatomical therapeutic chemical (ATC) codes (e.g., DM with insulin use was validated by insulin use >60 days before operation, ATC code of insulin: A10A). The diagnosis of acute coronary syndrome (ACS) should fulfill the following criteria: (1) specific ICD-9 CM code of ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), and unstable angina; and (2) record of emergency room visit 48 h before the index PCI. The use of aspirin, clopidogrel, PPI, ACEI/ARB, β-blockers, and statins was identified (by ATC code) if the patient has used these drugs >60 days in 1 year before the index PCI.

All outcomes were assessed in the study cohort after the index PCI. We used ICD-9-CM codes or operation codes for composite primary outcomes including mortality, non-fatal MI, non-fatal stroke, and revascularization after the index procedure. Secondary outcomes were mortality, non-fatal MI, non-fatal stroke, and revascularization, CV death, hospitalization for heart failure, peptic ulcer disease or blood transfusion, respectively. CV death was defined according to the criteria of the Standardized Definitions for End Point Events in Cardiovascular Trials published

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**Figure 1.** Subject selection in end-stage renal disease (ESRD) patients on dialysis undergoing percutaneous coronary intervention (PCI). BMS, bare-metal stent; DES, drug-eluting stent.
DES vs. BMS Implantation in ESRD Patients

Results

Baseline Characteristics

By the Food and Drug Administration. We also assessed the type and condition of antiplatelet therapy at the onset of primary and secondary outcomes in these 2 groups. The follow-up period was defined as the index procedure to the date of death, loss of follow-up, or until 31 December 2012. The ICD9-CM codes are listed in Supplementary Table 1.

The CV outcomes between various DES generations were also analyzed. First-generation DES consisted of sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES); the second-generation DES consisted of everolimus-eluting stent (EES) and zotarolimus-eluting stent (ZES); and the third-generation of DES consisted of bioabsorbable polymer or polymer-free DES.

All outcomes were adjusted for clinical confounders, including gender, Charlson’s comorbidity index, prior history of CABG, number of stents per patient in the index procedure, and cumulative dosage (defined daily dose, DDD) of aspirin, clopidogrel, β-blockers, ACEI/ARB, and statins after onset of the index procedure (Supplementary Table 2).

Statistical Analysis

Categorical variables are presented as n (%), and continuous variables as mean ± SD. The demographic variables with standardized difference >0.1 between the DBS and BMS groups were considered have clinically significant differences. The cumulative DDD of aspirin, clopidogrel, β-blockers, ACEI/ARB, and statins after onset of the index procedure was considered as a time-dependent covariate.

Cox proportional hazard regression modeling with time-dependent covariate was used to estimate hazard ratios (HR) and 95% CI for all outcomes. All variants with significant difference (P<0.05) on univariate analysis were entered into the multivariate model. On multivariate analysis, P<0.05 was interpreted as statistically significant. All statistical analysis was performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

Table 1. ESRD Patient Baseline Characteristics After 1:1 Propensity Score Matching

<table>
<thead>
<tr>
<th></th>
<th>DES (n=1,151)</th>
<th>BMS (n=1,151)</th>
<th>Standardized difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>696 (60.5)</td>
<td>682 (59.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.7±10.3</td>
<td>65.1±10.5</td>
<td>−0.04</td>
</tr>
<tr>
<td>DM with insulin</td>
<td>57 (5.0)</td>
<td>54 (4.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>DM without insulin</td>
<td>652 (56.7)</td>
<td>652 (56.7)</td>
<td>0.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,117 (97.1)</td>
<td>1,129 (98.1)</td>
<td>−0.07</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>871 (75.7)</td>
<td>870 (75.6)</td>
<td>0.00</td>
</tr>
<tr>
<td>Duration of ESRD (years)</td>
<td>4.4±4.0</td>
<td>4.1±3.8</td>
<td>0.09</td>
</tr>
<tr>
<td>ACS ≤48h before index PCI</td>
<td>164 (14.3)</td>
<td>146 (12.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior MI</td>
<td>134 (11.6)</td>
<td>132 (11.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>3 (0.3)</td>
<td>3 (0.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>513 (44.6)</td>
<td>517 (44.9)</td>
<td>−0.01</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>707 (61.4)</td>
<td>713 (62.0)</td>
<td>−0.01</td>
</tr>
<tr>
<td>No. stents per patient in the index procedure</td>
<td>1.09±0.33</td>
<td>1.09±0.32</td>
<td>−0.01</td>
</tr>
<tr>
<td>1</td>
<td>1,058 (91.9)</td>
<td>1,054 (91.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>82 (7.1)</td>
<td>88 (7.6)</td>
<td>−0.04</td>
</tr>
<tr>
<td>3</td>
<td>9 (0.8)</td>
<td>7 (0.6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Medication before procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>550 (47.8)</td>
<td>536 (46.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>288 (25.0)</td>
<td>279 (24.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Statins</td>
<td>540 (46.9)</td>
<td>562 (48.8)</td>
<td>−0.04</td>
</tr>
<tr>
<td>β-blockers</td>
<td>657 (57.1)</td>
<td>656 (57.0)</td>
<td>0.00</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>590 (51.3)</td>
<td>586 (50.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>PPI</td>
<td>238 (20.7)</td>
<td>239 (20.8)</td>
<td>0.00</td>
</tr>
<tr>
<td>Medication after discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1,069 (92.9)</td>
<td>1,047 (91.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1,146 (99.6)</td>
<td>1,141 (99.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Statins</td>
<td>788 (68.5)</td>
<td>736 (63.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>β-blockers</td>
<td>959 (83.3)</td>
<td>916 (79.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>865 (75.2)</td>
<td>843 (73.2)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data given as mean ± SD or n (%). ACS, acute coronary syndrome; ACEI/ARB, angiotensin-converting enzyme/aldosterone receptor blocker; BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; DM, diabetes mellitus; ESRD, end-stage renal disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.
After adjustment on multivariate regression, composite primary outcomes (i.e., mortality, non-fatal MI, non-fatal stroke, and revascularization) were similar between the groups (HR, 0.94; 95% CI: 0.81–1.09, P=0.399; Table 2: Figure 2). Secondary outcomes (i.e., mortality, non-fatal MI, non-fatal hemorrhagic stroke, non-fatal ischemic stroke, revascularization, CV death, heart failure, PUD, PUD with bleeding, blood transfusion) were similar between the groups (HR, 0.93–1.11; 95% CI: 0.79–1.27, P=0.52–0.81; Table 2).

Figure 2. Kaplan-Meier survival curves of (A) primary composite endpoint, (B) cardiovascular (CV) death, (C) non-fatal myocardial infarction (non-fatal MI), and (D) coronary revascularization in end-stage renal disease patients after implantation of bare-metal stent (BMS) or drug-eluting stent (DES).
DES vs. BMS Implantation in ESRD Patients

Consisted of acetylsalicylic acid (aspirin) and clopidogrel. Cilostazol was only occasionally used. Ticagrelor and prasugrel were not available at the time of the study. Dual antiplatelet therapy was used more in the DES group at the onset of primary outcome (66.2% in DES vs. 57.7% in BMS, standardized difference, 0.18).

Subgroup Analysis: Outcome vs. Generation of DES
Of the patients undergoing DES in the index procedure, MI, non-fatal stroke, and revascularization, CV death, hospitalization for heart failure, peptic ulcer disease and blood transfusion) were also similar between the groups, except for peptic ulcer disease, which had a lower risk in the DES group (HR, 0.59; 95% CI: 0.41–0.83, P=0.003) than in the BMS group.

The type and condition of antiplatelet therapy at the onset of primary and secondary were analyzed and are listed in Supplementary Table 3. Antiplatelet agents mainly consisted of acetylsalicylic acid (aspirin) and clopidogrel. Cilostazol was only occasionally used. Ticagrelor and prasugrel were not available at the time of the study. Dual antiplatelet therapy was used more in the DES group at the onset of primary outcome (66.2% in DES vs. 57.7% in BMS, standardized difference, 0.18).

**Table 3. Outcome in Dialysis Patients: DES Generation vs. BMS**

<table>
<thead>
<tr>
<th></th>
<th>First-generation DES (n=289)</th>
<th>Second-generation DES (n=702)</th>
<th>Third-generation DES (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes†</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.89 (0.72–1.10)</td>
<td>0.281</td>
<td>0.94 (0.79–1.13)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.88 (0.66–1.19)</td>
<td>0.422</td>
<td>0.99 (0.75–1.30)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.75 (0.47–1.21)</td>
<td>0.242</td>
<td>1.12 (0.75–1.69)</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>0.91 (0.69–1.20)</td>
<td>0.504</td>
<td>0.98 (0.77–1.25)</td>
</tr>
</tbody>
</table>

†Mortality, non-fatal MI, non-fatal stroke, and revascularization after the index procedure. Abbreviations as in Tables 1,2.

**Figure 3.** Kaplan-Meier survival curves of (A) primary composite endpoint, (B) cardiovascular (CV) death, (C) non-fatal myocardial infarction (non-fatal MI), and (D) coronary revascularization in end-stage renal disease patients vs. generation of drug-eluting stent (DES) or bare-metal stent (BMS) implantation.
289 (25.1%) received the first-generation SES and PES, 702 patients (60.9%) received the second-generation EES and ZES; and 116 patients (10.8%) received the third-generation stents. As compared with the BMS group, there were no significant differences in the composite primary outcomes of mortality, non-fatal MI, non-fatal stroke and coronary revascularization at 6-year follow-up in the DES subgroups (Table 3; Figure 3).

Discussion

In this well-designed, large-scale population-based cohort study, we found that the mortality, adverse cardiac events and repeat revascularization rates after PCI were very high in patients with ESRD under hemodialysis. The CV outcomes were similar between the DES and BMS groups. In the present study, the mortality rates were as high as 31.1% in the DES group and 39.2% in the BMS group during 6-year follow-up. These findings were consistent across all generations of DES compared with BMS, and have not been previously reported. The bleeding complications were also similar in both groups, although the incidence of peptic ulcer disease was higher in the BMS group. The longer follow-up period with a maximum of 6.0 years was achieved by linking nationwide databases in Taiwan, which provided real-world data on long-term outcomes for ESRD patients undergoing DES and BMS implantation.

The use of DES in ESRD patients is recommended in the current guideline, but the recommendations were based on observational studies and extrapolation of data from patients with normal renal function.6,10-12 The results of the observational studies, however, were heterogeneous: some showed that DES was superior to BMS,8-11 13 whereas others did not.16-20 The inconsistent results from the observation studies may be due to small cohort size, short-term follow-up, or lack of adequate adjustment for potential confounders. One recent meta-analysis evaluated current evidence for the efficacy and safety of DES and BMS in dialysis patients.7 The meta-analysis concluded that patients with DES may have better outcomes of all-cause mortality, target vessel revascularization (TVR), and target lesion revascularization (TLR) compared with the BMS group, but the outcome of MI did not decrease. The studies in the meta-analysis, however, were not randomized and therefore selection and allocation bias cannot be avoided. The treatment of CAD in patients with ESRD should ideally be based on evidence from randomized, clinical trials, but patients with ESRD were frequently excluded from the trials.11 There was only 1 randomized controlled trial (RCT) that did not exclude patients with ESRD on dialysis, and that study demonstrated a reduction of repeat revascularization in patients with reduced renal function and multivessel CAD undergoing EES implantation.22 But only 36 participants in that trial had ESRD,22 and the 1-year mortality rate was much lower in than previous studies.21-23 Therefore, those results may not be generalizable to the overall ESRD population.

In the present study, the 2 treatment groups were well-balanced with regard to baseline characteristics and procedure-related factors after 1:1 propensity score matching, such as stent number, disease condition (such as ACS or stable angina), and disease severity (Charlson’s comorbidity scores). Moreover, all results were adjusted using multiple important confounders to minimize potential bias. We used strict definitions for all pre-specified confounders to ensure accurate interpretation. Important drug exposure was defined as cumulative dosage (DDD) of antiplatelets, β-blockers, ACEI/ARB, statins and PPI in order to adjust for the effect of drugs on outcome. We used hard end-points including mortality, non-fatal MI, non-fatal stroke and repeat revascularization including repeat PCI or CABG as the primary outcomes. After matching and fully adjusting all confounders, the benefit of DES was not shown in the present study. The mortality rates were similar in both groups, and similar to previous results of large-scale cohort studies.6,8-10

The different generations of DES have different effectiveness in the prevention of restenosis, and safety for risks of stent thrombosis and MI. The introduction of new-generation DES such as EES or ZES may produce better clinical outcomes in non-dialysis patients,8 but very few studies have reported on the clinical outcomes of new-generation DES (ZES or EES) in dialysis patients. Most studies analyzed the performance of first-generation DES and SES vs. BMS in dialysis patients.15-20,22-25 Data on major adverse cardiac events and restenosis rate were inconsistent due the retrospective design and small sample size in those studies. To the best of our knowledge, this study is the first to evaluate the performance of various generations of DES in dialysis patients. We did not, however, find any significant difference in adverse cardiac events or coronary revascularization in patients treated by new-generation DES or even polymer family DES compared with BMS.

The possible reasons for the failure of DES implantation, including of newer generations of DES, to improve adverse cardiac event rates in patients with dialysis are complex: first, there were large burdens of comorbidities that may affect the response to and duration of drug therapy. Especially in patients undergoing antiplatelet therapy, there were fewer evident cardiac symptoms to draw physician attention, and there were fewer aggressive treatment strategies that could be chosen by care providers.26 Second, there exist marked differences in the formation of plaque in patients under hemodialysis compared with controls. Patients under hemodialysis tend to have much more heavily calcified and inflamed plaques. In addition to classic risk factors, disease-specific factors such as uncontrolled hyperphosphatemia and high calcium phosphate product, high oxidative stress, uremic toxin accumulation, exposure to bio-incompatible dialysis membranes and/or contaminated dialysis fluid and novel risk factors such as infection, hyperhomocysteinemia, and accumulation of the endogenous inhibitor of NO synthase, asymmetric dimethylarginine all contribute to an accelerated atherosclerosis process in dialysis patients. The aforementioned factors cannot be overcome by using DES and perhaps contribute to the worse clinical outcome in patients under hemodialysis.27,28 Third, patients on hemodialysis tend to have diffuse multivessel and rigid calcified coronary artery, which can impede the delivery and adequate expansion of different stents.27-28 Positioning, adequate deployment and post-dilatation may be more difficult in patients under hemodialysis because of severe calcifications. The assessment of optimal stent expansion may be more important in patients under hemodialysis because the newer stents are thinner and longitudinal compression may be a problem. And fourth, there is a high risk for serious bleeding events in hemodialysis patients due to uremia-induced platelet dysfunction and chronic antiplatelet use during hemodialysis.
Because of bleeding issues, hemodialysis patients are more likely to discontinue dual antiplatelet therapy, which may exacerbate the risk of stent thrombosis and MI. Severe endothelial dysfunction, enhanced platelet activation, and poor response to antiplatelet drugs contribute to the poor outcome after DES implantation in hemodialysis patients.\(^{29-31}\)

Due to the aforementioned reasons, the benefit of DES treatment was not shown in the present study; and this result is not unique to the present study: hemodialysis still remains a significant predictor of MACE, even with the use of newer generations of DES.\(^{32}\)

**Study Limitations**

There were some inherent limitations when using the NHIRD. First, some common confounders were not included, such as the severity and complexity of the diseased coronary arteries (left main coronary artery, chronic total occlusion, bifurcation lesions, and SYNTAX score); the procedure details (total stent length, and stent diameter); or the clinical variables (e.g., left ventricular ejection fraction). Second, there were no data on follow-up angiography, meaning that we were unable to identify TVR, TLR, or de novo revascularization. Third, there are no data on stent thrombosis after stenting or any procedure-related complications in NHIRD. This information may affect the results, despite the use of comprehensive analytical strategies to test the robustness of the results. Although we adjusted for confounders using Cox proportional hazard regression analysis, the retrospective nature of this study limits some of the conclusions that can be derived from the data. In the absence of randomization to DES or BMS, the potential bias for residual confounding still remains in this study.

**Conclusions**

In this nationwide large cohort study, the mortality rates were high in both the DES and BMS groups, suggesting that dialysis patients undergoing PCI with DES implantation might not have better clinical outcomes than dialysis patients with BMS implantation during a relative long-term follow-up period. Although the newer generation of DES may look appealing, the use of DES did not have the desired effect, despite the use of antiplatelet drugs. This information may affect the results, despite the use of comprehensive analytical strategies to test the robustness of the results. Although we adjusted for confounders using Cox proportional hazard regression analysis, the retrospective nature of this study limits some of the conclusions that can be derived from the data. In the absence of randomization to DES or BMS, the potential bias for residual confounding still remains in this study.

**Disclosures**

The authors declare no conflicts of interest.

**References**


**Supplementary Files**

Please find supplementary file(s);