Long-Term Clinical Outcome of Chronic Total Occlusive Lesions Treated With Drug-Eluting Stents
– Comparison of Sirolimus-Eluting and Paclitaxel-Eluting Stents –

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**Background:** There are few studies comparing the efficacy of different drug-eluting stents and their long-term clinical outcomes in percutaneous coronary intervention (PCI) of chronic total occlusive (CTO) lesions.

**Methods and Results:** To compare the efficacy of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) for CTO, and to identify predictors of outcome after PCI, 200 patients with at least 1 successfully revascularized CTO were enrolled into either a SES (n=132) or PES (n=71) group. At 6–9-month angiographic follow-up, SES was superior to PES (late loss 0.27±0.60 vs 0.53±0.62 mm, P=0.04). During mean follow-up of 2 years, the SES group had a significantly lower cumulative target vessel failure (TVF) rate than the PES group (14.9% vs 28.4%, P<0.01), as a consequence of lower target vessel revascularization (9.7% vs 23.9%, P<0.01) and a partially lower rate of myocardial infarction (MI: 3.1% vs 7.6%, P=0.04). SES was also superior to PES in both early (<9 months) and late (>9 months) TVF (P=0.02 for log-rank test, respectively). Predictors for TVF were use of PES (hazard ratio (HR) 3.81, P<0.01), previous history of MI (HR 4.06, P<0.01), diabetes (HR 2.07, P=0.04) and chronic kidney disease (CKD; HR 3.56, P=0.05).

**Conclusions:** CTO lesions treated with SES showed better angiographic and long-term clinical outcomes than those treated with PES. Factors such as stent type, infarct-related CTO, diabetes and CKD affect the outcome of CTO intervention. (Circ J 2010; 74: 693–700)

**Key Words:** Angiographic outcome; Chronic total occlusion; Clinical outcome; Paclitaxel-eluting stent; Sirolimus-eluting stent

Chronic total occlusion (CTO) of a coronary artery is present in almost one-third of patients with coronary artery disease (CAD), and is a very common reason not to attempt percutaneous coronary intervention (PCI). Although PCI for CTO accounts for 10–20% of all PCI procedures, and complete revascularization of the CTO is more favorable for survival than an incomplete attempt, it has a lower success rate than for those of other de novo coronary lesions. Compared with plain old balloon angioplasty, bare metal stent (BMS) implantation has shown favorable results, but restenosis/re-occlusion resulting in target lesion revascularization (TLR) has remained a frequent and thus a major limitation.

Although drug-eluting stents (DES) have shown superior results in terms of major adverse cardiovascular events (MACE) compared with BMS in various angiographic pa-

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tient subsets\textsuperscript{13-15} and also in CTO lesions,\textsuperscript{16-20} there have been few studies comparing the results of different DES,\textsuperscript{21} namely, sirolimus-eluting stents (SES) and paclitaxel-eluting stent (PES) in CTO lesions particularly. In addition, the long-term clinical efficacy and clinical predictors of outcome after PCI of CTO with DES remains largely unknown. This study is the first to report comparative results of angiographic and long-term clinical efficacy of first-generation DES in CTO lesions.

**Methods**

**Study Population**
All patients in whom PCI was attempted for opening a CTO lesion were prospectively enrolled from July 2003 to April 2008 in the CTO registries of 2 centers, Seoul National University Hospital and Seoul National University Bundang Hospital. Patients received either a SES (Cypher\textregistered, Cordis Johnson & Johnson, Miami, FL, USA) or a PES (Taxus\textregistered, Boston Scientific Corp, Natick, MA, USA). The selection of equipment for the angioplasty, including the choice of DES, was left to the operators’ discretion.

This study was approved by the Institutional Review Board of Seoul National University Hospital and all patients gave informed consent to participate in the study.

**Definitions**
A CTO was defined as complete obstruction of the vessel with Thrombolysis In Myocardial Infarction antegrade flow 0 with an estimated duration $\geq 1$ month with or without visible collateral flow, whether antegrade or retrograde.\textsuperscript{16} All occlusions were located in a native vessel.

Target vessel failure (TVF) was defined as a composite of cardiac death, nonfatal myocardial infarction (MI), and target vessel revascularization (TVR). All deaths were considered as cardiac unless a specific cause of death was demonstrated. MI was defined as the presence of at least 2 of the following: ischemic symptoms, concentrations of cardiac enzymes (creatinine kinase and its MB isoenzyme, CK-MB) at least twice their upper normal limits, and new ECG changes compatible with MI. TVR was defined as any repeat PCI or coronary artery bypass graft surgery of the target vessel. Ischemia-driven TVR was defined as TVR attributable to typical ischemic symptoms or ischemic signs on stress testing. Complete revascularization was defined as residual stenosis $\leq 25\%$ on visual assessment of the 3 coronary arteries and their major branches with diameter $\geq 2$ mm by visual estimation, as defined in a previous report.\textsuperscript{3} Dyslipidemia was defined as current use of statins or initial low-density lipoprotein-cholesterol level $>160$ mg/dl. Chronic kidney disease (CKD) was defined as initial serum creatinine level $>1.5$ mg/dl.

**Interventional Procedure and Pharmacotherapy**
All PCI procedures were performed using standard techniques and various guidewires were used to cross the lesions. After pre-dilatation, stents were deployed, and if necessary, adjunct high-pressure balloon dilatation was performed to achieve angiographic optimization (residual diameter stenosis $<25\%$). All patients were pretreated with aspirin and clopidogrel (a loading dose of 300 mg at least 6 h before the procedure). After the procedure, all patients were given aspirin (at least 100 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 1 year. Use of glycoprotein IIb/IIIa inhibitors was left to the operator’s discretion.

**Angiographic Analysis**
Angiographic analysis was done on end-diastolic frames demonstrating the stenosis in its most severe view. The view with the least foreshortening was selected for the analysis, which was done with CASS QCA for Research 2.0.1 (Pie Medical Imaging, Maastricht, The Netherlands) and standard morphologic criteria were used for the analysis of the entire treated segment. Post-procedure reference vessel diameter (RVD) and minimal lumen diameter (MLD) were calculated. Follow-up angiography was recommended to all patients at 6–9 months after the index procedure. Late luminal loss (LL) was calculated by subtracting follow-up MLD from post-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{flowchart.png}
\caption{Flowchart of the patients throughout the study. CTO, chronic total occlusion; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent.}
\end{figure}
Long-Term Outcomes of DES in CTO

procedure MLD. Binary restenosis was considered as >50% diameter stenosis within the target lesion.

Clinical Follow-up and Database Management
Patients were followed up for clinical events, and evaluated for development of TVF using medical records, questionnaires and telephone enquiries. All data input was done by research nurses and database managers who were unaware of the purpose of the study.

Statistical Analysis
Continuous variables, presented as mean±SD, were compared by unpaired Student’s t-test. Categorical variables, presented as frequency and percentages, were compared using the Chi-square test or Fisher’s exact test as appropriate. TVF-free survival curves were drawn using the Kaplan-Meier method and the log-rank test was used to compare survival between 2 groups. Multivariate analyses were performed using a Cox proportional hazards model. All baseline clinical characteristics, together with the type of stent and stent length, were initially included for analysis. When verifying the analyses results with stepwise forward or backward Cox’s regression, a P-value of 0.10 was used to exclude or include the variables. A P-value <0.05 was considered statistically significant. All statistical analyses were performed with the use of SPSS 17.0 software (SPSS Inc, Chicago, IL, USA).

Results

Baseline Characteristics of the Study Population
We enrolled 260 patients with at least 1 CTO lesion in the combined registry. CTO PCI failed in 58 of these patients, so 202 patients who were successfully revascularized were included in this study. Among them, 5 had 2 CTO lesions that were treated simultaneously and 2 patients were excluded from the final analysis because the lesions were treated with a combination of different types of stents. In total, 203 CTO lesions from 200 patients were included in the final analysis (Figure 1).

Baseline clinical characteristics of the patients are shown in Table 1. There were no significant differences between the 2 groups, including age, gender, diabetes mellitus (DM) and

Table 1. Baseline Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Total (n=200)</th>
<th>SES (n=130)</th>
<th>PES (n=70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.2±9.5</td>
<td>63.2±9.9</td>
<td>63.3±9.0</td>
<td>0.93</td>
</tr>
<tr>
<td>Male (%)</td>
<td>74.0</td>
<td>75.4</td>
<td>71.4</td>
<td>0.61</td>
</tr>
<tr>
<td>DM (%)</td>
<td>36.0</td>
<td>37.7</td>
<td>32.9</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59.5</td>
<td>56.2</td>
<td>65.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>19.0</td>
<td>16.9</td>
<td>22.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>25.0</td>
<td>23.1</td>
<td>28.6</td>
<td>0.40</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>5.0</td>
<td>6.2</td>
<td>2.9</td>
<td>0.50</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>20.0</td>
<td>20.8</td>
<td>18.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.2±13.0</td>
<td>55.3±12.4</td>
<td>55.1±14.2</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Data are mean values±SD or %. SES, sirolimus eluting stent; PES, paclitaxel-eluting stent; DM, diabetes mellitus; CKD, chronic kidney disease; MI, myocardial infarction.

Table 2. Angiographic Characteristics at Baseline and at Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>SES</th>
<th>PES</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occluded artery (n=203)</td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>LAD</td>
<td>48.3</td>
<td>49.2</td>
<td>46.5</td>
<td></td>
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<tr>
<td>LCX</td>
<td>18.7</td>
<td>17.4</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>33.0</td>
<td>33.3</td>
<td>32.4</td>
<td></td>
</tr>
<tr>
<td>Disease extent (n=200)</td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>26.0</td>
<td>27.7</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>39.0</td>
<td>41.5</td>
<td>34.3</td>
<td></td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>35.0</td>
<td>30.8</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td>No. of stents (n=203)</td>
<td>1.5±0.7</td>
<td>1.5±0.7</td>
<td>1.6±0.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td></td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Initial index procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>2.79±0.39</td>
<td>2.80±0.36</td>
<td>2.76±0.44</td>
<td>0.61</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.62±0.43</td>
<td>2.64±0.42</td>
<td>2.56±0.43</td>
<td>0.27</td>
</tr>
<tr>
<td>6–9-month follow-up (n=117)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MLD (mm)</td>
<td>2.23±0.74</td>
<td>2.36±0.71</td>
<td>1.96±0.73</td>
<td>0.01</td>
</tr>
<tr>
<td>Late LL (mm)</td>
<td>0.35±0.61</td>
<td>0.27±0.60</td>
<td>0.53±0.62</td>
<td>0.04</td>
</tr>
<tr>
<td>Binary restenosis (%)</td>
<td>9.6</td>
<td>6.3</td>
<td>16.7</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data are mean values±SD or %. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; RVD, reference vessel diameter; MLD, minimal luminal diameter; LL, luminal loss. For other abbreviations, see Table 1.
previous history of MI. In addition, there was no difference in the medications (angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, \( \beta \)-blocker, statins, medications for DM) of the 2 groups, except for a tendency for more use of calcium-channel blockers in the PES group (P=0.05).

**Angiographic and Procedural Variables**

A summary of the procedural characteristics is presented in Table 2. In total, 201 SES (Cypher\textsuperscript{®}) were implanted in 130 patients, and 111 PES (Taxus\textsuperscript{®}) in 70 patients. Almost all patients in both groups received complete revascularization (96.2% in SES vs 97.1% in PES group, P=1.00). There were no differences in lesion location or extent of CAD. There were no significant differences in the 2 groups in terms of post-procedure RVD or MLD, number of stents deployed, or stented length.

A total of 117 lesions (=58%) were available for follow-up angiography at 6–9 months after stent implantation. In-stent MLD, and late LL showed significantly favorable outcomes in the SES group compared with the PES group (P=0.01 for MLD, and P=0.04 for late LL, respectively). There was also a favorable trend towards SES in terms of binary restenosis rate (P=0.08) (Table 2).

**Long-Term Clinical Follow-up and Outcomes**

At a mean of 2 years’ follow-up, 18 patients in the SES group and 19 patients in the PES group experienced TVF. A summary of clinical outcomes is shown in Table 3. Out-of-hospital clinical outcomes for over 1 year were available in 90% of the patients. The mean duration of follow-up was 856\( \pm \)378 and 769\( \pm \)342 days for the SES and PES groups, respectively (P=0.10). In addition, the day of TVF was calculated from the day of index procedure (Figure 2): there were 2 phases in the curve of the incidence of TVF; a steep
increase of incidence in the early period and a mild increase in the later one. Among a total of 37 patients who experienced TVF, 54% of events occurred within 9 months and the remaining 46% occurred after 9 months. Among patients who experienced TVF after 9 months (n=16), more than half experienced TVR 2 years after the index procedure (n=12). The cumulative TVF rate was 14.9% and 28.4% for the SES and PES groups, respectively (P=0.01). Intriguingly, this difference was mainly driven by the significant lower rate of TVR and partially by the lower rate of MI in the SES group (P=0.01 for TVR and P=0.04 for MI). However, there were no statistically-significant differences between both groups in the rate of cardiac death (Table 3). Overall, the TVF-free survival rate was significantly better in the SES group than in the PES group (Figure 3A).

Three approaches were used to eliminate the effect of ‘occulostenotic reflex’ by routine follow-up coronary angiography at 6–9 months. First, we performed a landmark analysis starting from 9 months, and separately analyzed the subgroup of patients who experienced TVF after 9 months post-PCI. A total of 16 patients experienced TVF after 9 months, 9 in the SES group and 7 in the PES group (Table 3). As described earlier, more than half of these events were attributed to TVR. When analyzed for late TVF incidence, there was a significant difference between the 2 groups (P=0.02 for log-rank test) (Figure 3B).

Our second approach was to analyze the subgroup of patients who underwent unscheduled coronary angiography before 9 months or refused routine coronary angiography at 6–9 months. A total of 85 patients (42.5% of all patients) met these criteria. Overall, 14 cases of TVF occurred in this subgroup (Table 4). The SES group showed clinical superiority compared with the PES group (P=0.01), which was largely driven by the reduction in TVR (P=0.01) rather than by MI or cardiac death.

Third, we analyzed patients who underwent TVR because...
Predictors of MACE After Successful PCI of CTO Lesions

To identify independent predictors of TVF in CTO lesions after successful PCI with a DES, multivariate Cox’s regression analysis was performed for all baseline characteristics. Significant independent predictors of TVF following PCI for CTO lesions were: (1) previous history of MI (hazard ration [HR] 4.06, P<0.01), (2) DM (HR 2.07, P=0.04), (3) use of PES (HR 3.81, P<0.01) and (4) CKD (HR 3.56, P=0.05) (Table 5). Of these, type of stent and previous history of MI were the most significant predictors. When analyzed with ischemia-related TVF as the endpoint, significant predictors of TVF were: (1) previous history of MI (HR 3.65, P<0.01), (2) CKD (HR 6.05, P=0.01) and (3) use of PES (HR 2.85, P=0.05).

Discussion

Together with the treatment of diffuse multivessel disease and in-stent restenosis lesions, treatment of CTO lesions is considered as 1 of the remaining major challenges facing interventional cardiologists and the treatment strategy of multivessel disease is currently affected by the presence of CTOs. According to a report, 73% of patients without a CTO are referred to PCI, but in the presence of CTO only 47% are referred.

In the era of BMS, several studies reported that PCI of CTO had a low success rate and high incidence of restenosis. However, opening of total coronary occlusions can be beneficial, restoring blood flow to hibernating myocardium and thus improving symptoms and left ventricular function. Although there has been the rare case report of good survival of patient with CTO with only medical treatment, it is generally suggested that successful revascularization of CTO lesions has a survival advantage compared with failed revascularization.

After the introduction of DES, several studies demonstrated that the new stents markedly reduced the incidence of both angiographic restenosis and repeat revascularization in selected patients with relatively noncomplex lesions. In patients with CTO lesions, there are a few comparisons of the efficacy of DES with BMS and all have shown the superiority of DES over BMS in terms of 6–9-month angiographic follow-up. Clinical reports including up to 1-year clinical follow-up have also shown that DES are superior to BMS, thereby supporting the angiographic data.

Superiority of SES to PES in CTO Lesions

Although the superiority of DES over BMS in reducing repeat revascularization in CTO lesions is generally accepted, there is a paucity of data on whether there is a difference among the DES. In the present study, we found that SES had a more favorable long-term outcome in reducing the occurrence of TVF, mostly driven by a reduction in TVR.

Previous reports have demonstrated that routine coronary angiography after PCI increases TVR. To analyze and eliminate the effect of the ‘oculostenotic reflex’ associated with routine 6–9 months coronary angiography follow-up, we analyzed our data using 3 different approaches. In the subgroup of patients who refused routine follow-up or those who underwent unscheduled coronary angiography, and also in the subgroup who experienced TVF after the routine coronary angiography follow-up period, the SES group showed favorable outcomes compared with the PES group. In addition, a composite of ischemia-driven events, cardiac death, MI and ischemia-related TVR also showed a trend for a difference between SES and PES. We believe that all the rigorous analyses of our data point to a benefit of SES compared with PES in reducing TVF in CTO lesions.
In light of the importance of complete revascularization of CTO lesions, there is a possibility that the outcome of the 2 stent groups in the present study was confounded by the difference in successful complete revascularization rates. However, there was no difference between the 2 groups in the percentages of patients who were completely revascularized and we believe that this possibility can be ruled out. In addition, the possibility of drugs as a possible bias influencing the outcome of both stents can also be ruled out because the drugs used in both groups were not different.

The superiority of SES has been demonstrated in other subsets of patients or lesions, albeit with some controversy. The results of a meta-analysis of 6 randomized head-to-head clinical trials, in which a total of 3,669 patients were randomly assigned to either SES or PES, found significant differences in rates of restenosis (9.3% vs 13.1%, P<0.001) and TLR (5.1% vs 7.8%, P<0.001), favoring SES; however, no significant differences were found in mortality, MI, or stent thrombosis rates between the study groups. Similar findings have been reproduced in another meta-analysis of a pooled analysis of 16 randomized trials. Our data corroborate these previous findings and extend the observations to CTO lesions (ie, SES may be superior to PES in terms of repeat revascularization, but not with regard to cardiac death rates).

‘Delayed Phenomenon’ of TVF Occurrence After CTO Intervention With DES

Our study is unique in providing an understanding of the long-term clinical behavior of CTOs after intervention with a DES. To our knowledge, there have been very few reports of such long-term results for CTO lesions in the era of DES. Especially a comparison of the efficacy of the most widely used DES, namely SES and PES. None of the previous reports have compared efficacy in terms of either angiographic or clinical parameters of the 2 main types of stent in the long term (>1 year).

With an overall mean follow-up of 2 years, 54% of all TVF occurred within 9 months, and the remaining 46% occurred after 9 months post index procedure. This finding matches registry results from the BMS era in which TVF-free survival rates continued to decrease even 1 year after successful revascularization. This ‘delayed phenomenon’ of TVF after CTO intervention suggests an underestimation of the TVF rate in the short-term follow-up. In fact, in a previous report in which the outcomes were presented for only 1 year, the TVF rate (5%) was lower than in our study (20%) with a longer follow-up duration (mean 2 years).

The long-term clinical benefit of SES, even after 9 months, compared with PES (8.5% vs 13.2%, P=0.02 for log-rank test) was a composite of benefit in terms of MI and TVF, suggesting that not just a single outcome can explain this difference between the 2 types of DES. Although long-term comparative data for SES and PES in other lesion subsets are scarce, it has been demonstrated that SES shows better long-term clinical outcome in small vessels and in patients with DM. Our data suggest that CTO lesions may be another subset of patients who may benefit from SES implantation in the long-term.

Independent Predictors of TVF in CTO in the DES Era

According to our multivariate Cox regression analysis, PES use and a previous history of MI were strong significant predictors of a worse outcome. DM was also a significant predictor of TVF in CTO lesions, which is concordant with registry-based data from the BMS era. An interesting difference was that the data from Hoyer et al., which were mainly from the BMS data, showed that successful revascularization confers a better outcome irrespective of the presence of DM, whereas our results showed that the presence of DM still affects the patient’s outcome irrespective of complete and successful revascularization of the CTO. This slightly different finding may reflect the difference between DES and BMS in the context of DM, which has been verified in various subsets of lesions in diabetic patients. An additional interesting finding was that DM was not a significant predictor of ischemia-related MACE in contrast to the case of total MACE. This may be related to the typical ‘oculostenotic reflex’ in interventional cardiology, which may have contributed to overtreatment of stenotic lesions. Also, the insensitivity of DM patients to ischemic symptoms may have been a confounding factor.

CKD patients were also likely to experience TVF, which is also concordant with previous data that renal insufficiency raises the risk of MACE after PCI. CKD is a slowly progressive disease that is notorious for being associated with the poorest endothelial function and highly prevalent cardiovascular disease, for several reasons. This high-risk feature of CKD may have been a reason why CKD was such a strong predictor of late TVF in CTO lesions in the present study.

A previous history of MI was also a predictor of TVF, whether early or late or even ischemia-related, which is also concordant with various sets of clinical data. In particular, analysis of our data suggests that those with a prior history of MI have a significantly lower ejection fraction (<35%), which, in turn, is associated with a significant rate of TVF.

Study Limitations

This study was not a randomized trial but a registry with prospectively collected data from 2 centers’ cohorts. However, the operators used the identical interventional technique, irrespective of stent type. In addition, there was no significant difference in either clinical or angiographic baseline data. Angiographic follow-up was available in 58% of the patients, so additional events without symptoms, such as silent re-occlusion, cannot be excluded. However, the substantial absence of angiographic data was partially supplemented by our various analyses of the clinical data. In addition, long-term clinical follow-up for up to 2 years was achieved in nearly all of the patients.

Conclusion

When compared with PES, SES showed a significantly better outcome with regard to reducing the incidence of TVF in CTO lesions, even in the long-term, mainly because of a reduction in repeated revascularization but also partially by a reduction of the rate of MI. The occurrence of TVF after CTO intervention with DES can be divided into 2 phases: traditional restenosis-related events during the early period and a continuous occurrence of events in the later period. Clinical factors such as stent type, infarct-related CTO, DM, and CKD were significantly related with the long-term clinical outcomes of PCI of CTO.

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