Revascularization vs. Medical Therapy for Coronary Chronic Total Occlusions in Patients With Chronic Kidney Disease

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Background: We investigated whether the outcome of revascularization differed from the outcome of medical therapy in chronic kidney disease (CKD) and non-CKD patients with chronic total occlusion (CTO).

Methods and Results: A total of 2,010 patients with CTO who underwent revascularization (n=1,355), including percutaneous coronary intervention (PCI) or coronary artery bypass grafting (n=477), or had medical therapy alone (n=655) were examined. The primary outcome was all-cause death during follow-up. Among the non-CKD patients (n=1,679), revascularization had a lower incidence of all-cause death (adjusted hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.41–0.72, P<0.001) compared with medical therapy. Among the CKD patients (n=331), the difference in the incidence of all-cause death was not as marked between the 2 treatments (adjusted HR 0.71, 95% CI 0.48–1.06, P=0.09). There was a significant interaction between kidney function and treatment strategy (revascularization vs. medical therapy) on all-cause death (P for interaction=0.014).

Conclusions: Based on the clinical outcomes, in CTO patients with preexisting CKD, revascularization via PCI or bypass surgery might not be as effective as in non-CKD patients.

Key Words: Chronic kidney disease; Coronary chronic total occlusion; Medical therapy; Revascularization

Chronic kidney disease (CKD) is associated with an increased risk of death and cardiovascular events.1,2 Despite coronary revascularization via percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), CKD has been shown to strongly increase the risk of death and long-term cardiac adverse events in patients with coronary artery disease (CAD).3-6 Coronary chronic total occlusions (CTO) are commonly encountered in patients undergoing coronary angiography. Recent studies from a multicenter registry reported a prevalence of CKD as 10–25% in patients with CTO, and that CKD was an independent predictor of death and adverse cardiac events in CTO patients.7-9 Several observational studies have reported that successful revascularization of CTO is associated with significant changes in cardiac function and better clinical outcomes.9-13 However, to date, there are no data regarding whether the outcome of revascularization differs in CKD and non-CKD patients with CTO. Furthermore, the optimal treatment strategy for these patients has not been determined. Therefore, we investigated clinical outcomes after revascularization vs. medical therapy (MT) in CTO patients with or without CKD.

Methods

Study Population
Between March 2003 and February 2012, 2,024 consecutive CTO patients were enrolled in the Samsung Medical Center CTO registry. Inclusion criteria for the registry were: (1) at least 1 CTO lesion detected on diagnostic coronary angiography, and (2) symptomatic angina and/or a positive functional ischemia study. Exclusion criteria were: (1) previous history of CABG, (2) cardiogenic shock or cardiopulmonary resuscitation as an initial presentation, and (3) ST-segment elevation acute myocardial infarction (MI) during the preceding 48 h. A CTO lesion was defined as a coronary artery obstruction with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 for an estimated...
Treatment of CTO in Patients With CKD

duration >3 months. The duration of the occlusion was estimated as the interval from the last episode of acute coronary syndrome (ACS) or from the first episode of effort angina consistent with the location of the occlusion or previous coronary angiogram in patients with no history of ACS.14 The patient flow chart of the study is shown in Figure 1. Subjects were classified into non-CKD and CKD groups according to their baseline renal function. Each group was divided into the revascularization and MT groups according to the treatment strategy.

Before coronary angiography was performed, serum creatinine levels were obtained for determining baseline renal function according to age, and sex using the Modification of Diet in Renal Disease (MDRD) equation, which estimates glomerular filtration rates (eGFR).15 In this study, patients were classified into 2 groups: eGFR ≥60 mL/min/1.73 m² was categorized as the non-CKD group and eGFR <60 mL/min/1.73 m² defined CKD, consistent with CKD stages 3–5 of the National Kidney Foundation classification.16

Treatment Strategy
Optimal MT included antiplatelet medication, β-blockers, renin–angiotensin system blockade, nitrates, calcium-channel blockers, and aggressive lipid-lowering therapy. The dosages of all medications were maximized as allowed by heart rate, blood pressure, and side effects in the absence of justifiable relative contraindications. Revascularization of the CTO was accomplished by CABG or PCI with a drug-eluting stent, and each revascularization strategy was selected according to the patient’s and physician’s preferences. In cases of CABG for CTO, arterial grafting with off-pump coronary artery bypass was the preferred technique. Coronary interventions were performed using standard techniques. The decision to perform bilateral injection and a retrograde approach, in addition to the type of wire, microcatheter, and use of intravascular ultrasound and glycoprotein IIb/IIIa receptor inhibitor were at the discretion of the physician. All patients received loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) before the PCI unless they had previously received these antiplatelet medications. After the procedure, aspirin treatment was continued lifelong, and the duration of clopidogrel treatment was determined by the physician. Successful revascularization was defined as a final residual stenosis <20% of the vessel diameter with TIMI flow grade ≥2 after revascularization, as assessed by visual estimation of the angiograms by experienced interventional cardiologists blinded to patient data.

Data Collection
Clinical, angiographic, procedural, and outcome data were retrospectively collected by a trained study coordinator using a standardized case report form and protocol. Additional information was obtained by contacting the principal investigators and/or reviewing the hospital records, if necessary. All baseline and procedural cine coronary angiograms were reviewed and analyzed quantitatively at the angiographic core laboratory (Cardiac and Vascular Center, Samsung Medical Center, Seoul, Korea) with an automated edge-detection system (Centricity CA 1000, GE, Waukesha, WI, USA) using standard definitions.17 The Institutional Review Board at Samsung Medical Center approved the study protocol and waived the requirement for informed consent.

Study Outcomes and Definitions
The primary outcome was all-cause death during follow-up. The secondary outcomes were cardiac death, MI, target vessel revascularization (TVR), and major adverse cardiac events (MACE), defined as a composite of cardiac death, MI, and TVR with PCI or CABG during follow-up. All deaths were considered to be of cardiac cause unless a definite non-cardiac cause could be established. MI was defined as recurrent symptoms with new ECG changes compatible with MI or a cardiac marker level at least twice.
The upper limit of normal.\textsuperscript{18} TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel.

**Statistical Analysis**

Continuous variables were compared using Student’s t-test or the Wilcoxon rank-sum test when applicable. Categorical data were analyzed using Fisher’s exact test or the Chi-square test as appropriate. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. A Cox proportional hazard model was used to compare the risk of adverse cardiac events between the revascularization and MT treatments and between the non-CKD and CKD patients groups. Covariates that were either statistically significant (with P value ≤0.2) on univariate analysis or clinically relevant were included in the multivariable Cox regression models. To accommodate possible confounding in the results because of covariate imbalances among the 4 patients groups (non-CKD/revascularization, non-CKD/MT, CKD/revascularization, CKD/MT), we estimated propensity scores using all available variables measured before treating patients based on a multivariable multinomial logistic regression. The “twang” method used in the procedure relies on tree-based regression models, and uses 2 balance metrics (absolute standardized mean difference and Kolmogorov-Smirnov statistic) from 2 stopping rules (the mean of the covariates or maximum across the covariates). When the balance statistics are stabilized, the balance is deemed optimized and satisfactory, and the procedure stops. We then used weighted Cox proportional hazard models that were constructed using the inverse probability of treatment weighting (IPTW) approach with stabilized weights. We also tested for interaction on whether the presence of CKD influenced the treatment effect for revascularization vs. MT on the clinical outcomes. All tests were 2-tailed, and P<0.05 was considered to be statistically significant. All analyses were performed using R 3.1.0 (R foundation for Statistical Computing, Vienna, Austria).

**Results**

**Baseline and Procedural Characteristics**

Of the 2,024 patients in the registry, 2,010 were included in the final analysis and classified into the non-CKD group (n=1,679, 83.5%) or the CKD group (n=331, 16.5%). Of the non-CKD patients, 509 (30.3%) received MT and 1,170 (69.7%) underwent revascularization with either PCI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-CKD patients</th>
<th>CKD patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Revascularization (n=1,170)</td>
<td>Medical therapy (n=509)</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.2±11.2</td>
<td>64.7±11.3</td>
</tr>
<tr>
<td>Male</td>
<td>971 (83.0)</td>
<td>410 (80.6)</td>
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<tr>
<td>Medical history</td>
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<td>Diabetes mellitus</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>687 (58.7)</td>
<td>311 (61.1)</td>
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<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Current smoker</td>
<td>396 (33.8)</td>
<td>155 (30.5)</td>
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<tr>
<td>Previous MI</td>
<td>244 (20.9)</td>
<td>160 (31.4)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>217 (18.5)</td>
<td>160 (31.4)</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>82 (7.0)</td>
<td>44 (8.6)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.8±12.4</td>
<td>54.4±12.5</td>
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<tr>
<td>Estimated GFR</td>
<td>86.5±17.9</td>
<td>84.8±16.7</td>
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<tr>
<td>Non-ST-segment elevation ACS</td>
<td>272 (23.2)</td>
<td>71 (13.9)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>891 (76.2)</td>
<td>390 (76.6)</td>
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<tr>
<td>CTO vessel</td>
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<tr>
<td>LAD</td>
<td>493 (42.1)</td>
<td>125 (24.6)</td>
</tr>
<tr>
<td>LCX</td>
<td>383 (32.7)</td>
<td>170 (33.4)</td>
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<tr>
<td>RCA</td>
<td>570 (48.7)</td>
<td>292 (57.4)</td>
</tr>
<tr>
<td>Multi-CTO</td>
<td>251 (21.5)</td>
<td>70 (13.8)</td>
</tr>
<tr>
<td>Blunt stump</td>
<td>521 (44.5)</td>
<td>261 (51.3)</td>
</tr>
<tr>
<td>Bridging collateral</td>
<td>401 (34.3)</td>
<td>194 (38.1)</td>
</tr>
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<td>Calcification</td>
<td>209 (17.9)</td>
<td>85 (16.7)</td>
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<td>Collateral flow</td>
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<td>0</td>
<td>27 (2.3)</td>
<td>14 (2.8)</td>
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<td>1</td>
<td>222 (19.0)</td>
<td>107 (21.0)</td>
</tr>
<tr>
<td>2</td>
<td>485 (41.5)</td>
<td>214 (42.0)</td>
</tr>
<tr>
<td>3</td>
<td>436 (37.3)</td>
<td>174 (34.2)</td>
</tr>
<tr>
<td>Proximal or mid CTO</td>
<td>864 (73.8)</td>
<td>323 (63.5)</td>
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</tbody>
</table>

Values are mean±SD or n (%). ACS, acute coronary syndrome; CTO, coronary chronic total occlusions; CVA, cerebrovascular accident; GFR, glomerular filtration rate; LAD, left anterior descending artery; LCx, left circumflex artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SMD, standardized mean difference.
### Table 2. Clinical Outcomes in Non-CKD and CKD Patients (Original Data)

<table>
<thead>
<tr>
<th></th>
<th>Non-CKD patients</th>
<th>CKD patients</th>
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<tbody>
<tr>
<td></td>
<td>Revascularization (n=1,170)</td>
<td>Revascularization (n=185)</td>
</tr>
<tr>
<td></td>
<td>Medical therapy (n=509)</td>
<td>Medical therapy (n=146)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>Revascularization (n=185)</td>
<td>All-cause death</td>
</tr>
<tr>
<td></td>
<td>Medical therapy (n=146)</td>
<td>MACE*</td>
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<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>Unadjusted HR (95% CI)</td>
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<tr>
<td></td>
<td>P value</td>
<td>P value</td>
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<tr>
<td>All-cause death</td>
<td>88 (7.5)</td>
<td>49 (26.5)</td>
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<tr>
<td></td>
<td>88 (17.3)</td>
<td>52 (35.6)</td>
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<tr>
<td></td>
<td>(0.30–0.54)</td>
<td>(0.50–1.10)</td>
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<td></td>
<td>&lt;0.001</td>
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<td></td>
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<td>(0.47–1.17)</td>
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<td></td>
<td>Cardiac death</td>
<td></td>
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<tr>
<td></td>
<td>34 (2.9)</td>
<td>31 (16.8)</td>
</tr>
<tr>
<td></td>
<td>31 (6.1)</td>
<td>33 (22.6)</td>
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<tr>
<td></td>
<td>(0.27–0.72)</td>
<td>0.74</td>
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<tr>
<td></td>
<td>0.001</td>
<td>(0.45–1.20)</td>
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<td></td>
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<td>0.22</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td></td>
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<tr>
<td></td>
<td>8 (0.7)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td></td>
<td>3 (0.6)</td>
<td>8 (5.5)</td>
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<tr>
<td></td>
<td>(0.29–4.18)</td>
<td>0.49</td>
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<tr>
<td></td>
<td>0.88</td>
<td>(0.16–1.50)</td>
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<td></td>
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<td>0.21</td>
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<tr>
<td></td>
<td>TVR</td>
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<td></td>
<td>58 (5.0)</td>
<td>5 (2.7)</td>
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<td></td>
<td>40 (7.9)</td>
<td>5 (3.4)</td>
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<tr>
<td></td>
<td>(0.29–0.87)</td>
<td>0.78</td>
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<tr>
<td></td>
<td>0.001</td>
<td>(0.23–2.69)</td>
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</tbody>
</table>

Data are n (%). *MACE included cardiac death, recurrent MI, and TVR with PCI or coronary artery bypass graft. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

### Figure 2. Kaplan-Meier curves for clinical outcomes up to 5 years in the study population of patients with chronic total occlusions who underwent revascularization or received medical therapy.

(A,B) All-cause death and MACE in the non-CKD population. 
(C,D) All-cause death and MACE in the CKD population. CKD, chronic kidney disease; MACE, major adverse cardiac event.
(65.9%) or CABG (34.1%). Of the CKD group, 146 patients (44.1%) were treated with MT alone and 185 patients (55.9%) underwent revascularization (PCI 57.8%, CABG 42.2%). Baseline clinical and angiographic characteristics of the non-CKD and CKD patients who were treated with MT or underwent revascularization are shown in Table 1. Among the non-CKD patients, the MT group was older and had a significantly higher prevalence of a previous history of PCI and MI but lower prevalence of dyslipidemia and ACS than the revascularization group. The left ventricular ejection fraction was higher in the revascularization group. In the angiographic findings, the incidence of CTO in the left anterior descending coronary artery (LAD), multiple CTOs, and proximal to mid CTO lesions were significantly higher in the revascularization group than in the MT group. The SYNTAX score was also higher in the revascularization group. Among the CKD patients, the MT group was older and more likely to have a previous MI. Compared with patients who received MT, those who underwent revascularization were significantly more likely to have multiple CTOs, CTOs in the LAD, proximal to mid CTO lesions, and higher SYNTAX scores. Among the patients who underwent PCI, the residual SYNTAX score (8.71±9.4 vs. 6.00±8.21, P=0.005) and the ratio of residual SYNTAX scores >8 (39.3% vs. 28.5%, P=0.023) were higher in the CKD group than in the non-CKD group (8.71±9.4 vs. 6.00±8.21, P=0.005). The results of the IPTW method using the stabilized inverse propensity scores were checked to be in good balance. Overall, the balance was satisfactory in most covariates.

Clinical Outcomes
The median follow-up duration was 49.3 (interquartile range: 23.7–74.2) months and the cumulative incidences of the clinical outcomes are presented in Table 2. The success rate of PCI for CTO was significantly lower in the CKD group (non-CKD group 80.5% vs. CKD group 70.1%, P<0.012). The incidence of all-cause death according to clinical presentation (non-ACS vs. ACS) is shown in Figure S1.

Among the non-CKD patients, revascularization resulted in a lower incidence of all-cause death (7.5% vs. 17.3%, hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.41–0.72, P=0.001) than MT (Table 2, Figure 2A). After multivariable adjustment using Cox regression, this result was consistent (Table 3). Furthermore, results from the weighted Cox regression using the IPTW method had a similar outcome as the results using multivariable models in the non-CKD patients (Figure 2B). Among CKD patients, the incidence of all-cause death (26.5% vs. 35.6%, HR 0.71, 95% CI 0.48–1.06, P=0.09) did not show significant differences between the revascularization and MT groups (Table 2, Figure 2C). After adjustment for possible confounders, the adjusted risk of all-cause death did not differ significantly between the 2 groups and the result was again consistent when we applied a weighted Cox regression model using the IPTW method (Table 3).

When we assessed whether the magnitude of the treatment effects for revascularization and MT varied according to CKD status, we observed a significant interaction between CKD status and treatment strategy (revascularization vs. MT) for the endpoint of all-cause death: the interaction P value was 0.005. The success rate of PCI for CTO was significantly lower in the CKD group (non-CKD group 80.5% vs. CKD group 70.1%, P=0.012). The incidence of all-cause death according to clinical presentation (non-ACS vs. ACS) is shown in Figure S1.

Among the non-CKD patients, revascularization resulted in a lower incidence of all-cause death (7.5% vs. 17.3%, hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.41–0.72, P=0.001) than MT (Table 2, Figure 2A). After multivariable adjustment using Cox regression, this result was consistent (Table 3). Furthermore, results from the weighted Cox regression using the IPTW method had a similar outcome as the results using multivariable models in the non-CKD patients (Table 4). Among CKD patients, the incidence of all-cause death (26.5% vs. 35.6%, HR 0.71, 95% CI 0.48–1.06, P=0.09) did not show significant differences between the revascularization and MT groups (Table 2, Figure 2C). After adjustment for possible confounders, the adjusted risk of all-cause death did not differ significantly between the 2 groups and the result was again consistent when we applied a weighted Cox regression model using the IPTW method (Tables 3, 4).

Discussion
In this study, we sought to compare the clinical outcomes...
after revascularization vs. MT in patients with CTO according to the presence or absence of CKD. The major findings of this study were as follows. (1) In non-CKD patients, revascularization for CTO was associated with lower risks of all-cause death, cardiac death, TVR, and MACE compared with MT. (2) In patients with CKD, the incidence of all-cause death did not show significant differences between the revascularization and MT groups. Although the difference may be considered clinically significant, it is apparent that there was a significant interaction between CKD and all-cause death depending on the treatment strategy.

CKD is a common comorbid condition in patients with CAD and is associated with a higher risk of death and adverse cardiovascular events. Patients with CKD are more likely to have diffuse and accelerated atherosclerotic lesions, which is considered to be related to the increased prevalence of traditional risk factors such as hypertension, dyslipidemia and diabetes mellitus, as well metabolic and biochemical abnormalities such as systemic inflammation and hyperhomocysteinemia. Previous studies have evaluated the effect of CKD on clinical outcomes after PCI or surgical revascularization in patients with CAD. In general, the presence of CKD is associated with a lower success rate, a greater complication rate, and an increased risk of death and other adverse cardiac events after PCI. Prior studies have also shown that CKD is associated with worse in-hospital and long-term outcomes after surgical revascularization. Therefore, CKD has been regarded as a major prognostic factor for adverse outcomes in patients with CAD.

CTOs are prevalent and one of the most complex and challenging lesions in current interventional cardiology. Although it has not been proven by randomized trials, several observational studies have demonstrated that successful revascularization of CTOs can provide significant clinical benefits such as reduced death, MI, and need for CABG. Most of these studies have been conducted in Western countries, but Yang et al reported beneficial effects of CTO revascularization via PCI on all-cause death in Asian subjects. However, although CKD is a common condition in patients with CTO, most previous studies excluded or limited the enrollment of patients with significant CKD. Additionally, there have been no studies to date comparing differences in the long-term outcomes of MT vs. revascularization in CKD patients with CTO disease.

According to our analysis, revascularization of CTO lesions among the non-CKD population was associated with increased survival benefits similar to findings from previous studies. However, in patients with CKD, there were marginal differences between the revascularization and MT treatments in terms of clinical outcomes, including all-cause death, cardiac death, MI, and TVR. We also found that treatment effects of the 2 strategies (revascularization vs. MT) for patients with CTO were different in CKD and non-CKD patients with regard to all-cause death, including significant interactions. These results may be related to several factors. First, it has been reported that patients undergoing successful PCI for CTOs had lower rates of cardiac events than patients who had unsuccessful PCI. In the present study, we found that the rate of successful PCI for CTO was lower in patients with CKD than in non-CKD patients. Second, CKD is associated with proinflammatory and prothrombotic conditions, fatal stent thromboses, and fatal arrhythmias. These factors might drive the higher rate of death in the CKD group even when patients underwent successful revascularization.

Finally, we investigated whether the magnitude of the benefit of revascularization over MT was influenced by renal function using an interaction analysis. There were significant interactions between CKD status and treatment strategy on survival, suggesting that the superiority of revascularization over MT is dependent on renal function. Therefore, our findings will be helpful when making clinical decisions for patients with CTO and significant renal insufficiency.

**Study Limitations**

First, this was a retrospective and nonrandomized trial, so the selection of treatment modality was likely influenced by physician or patient preference, and otherwise unmeasured confounders or hidden biases may be present. Second, because of the retrospective nature of the registry, we could not thoroughly investigate the modification and discontinuation of cardioprotective agents in all study patients during follow-up. Third, estimated GFR was calculated by the MDRD equation in this study, which has been found to be more accurate, more precise, and less biased than the Cockcroft-Gault equation in patients with CKD undergoing PCI. However, misclassification bias is possible because we estimated GFR based on a single preprocedure creatinine measurement. Lastly, data on post-procedure creatinine or contrast-induced nephropathy were not available.

**Conclusions**

In CTO patients with preexisting CKD, revascularization via PCI or bypass surgery might not be as effective as in non-CKD patients. Additional large clinical trials are required to compare CTO revascularization with MT in these patients.

**Conflict of Interest**

The authors have no relationships to report that could be construed as conflicts of interest.

**References**


Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier curves for all-cause death in non-ACS and ACS patients.

Please find supplementary file(s):