Long-Term Clinical Outcomes of Medical Therapy for Coronary Chronic Total Occlusions in Elderly Patients (≥75 Years)

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**Background:** Limited data are available on the clinical outcomes of medical therapy (MT) compared with revascularization in elderly patients with coronary chronic total occlusion (CTO).

**Methods and Results:** Between March 2003 and February 2012, we retrospectively analyzed 311 patients aged ≥75 years in the Samsung Medical Center CTO registry. Among these, 153 patients were treated with MT and 158 patients with revascularization by intervention or surgery. Inverse probability of treatment weighting (IPTW) and propensity score-matching were performed. The primary outcome was cardiac death during follow-up. Median follow-up duration was 34 (interquartile range: 15–58) months. Overall, patients in the MT group were high-risk subjects. Cardiac death of 30 patients (19.6%) occurred in the MT group vs. 17 patients (10.8%) in revascularization group (P=0.027). In the multivariate analysis, there was no significant difference between groups in the rate of cardiac death (hazard ratio [HR], 1.67; 95% confidence interval [CI], 0.86–3.24, P=0.13). After adjustment with IPTW, MT showed comparable risk of cardiac death with revascularization therapy (HR, 1.26; 95% CI, 0.71–2.21, P=0.43). In the propensity score-matched population, there was no significant difference in the rate of cardiac death between the MT and revascularization groups (HR, 1.52; 95% CI, 0.76–3.07, P=0.24).

**Conclusions:** In the treatment of CTO in elderly patients, MT alone did not increase the risk of long-term cardiac death when compared with aggressive revascularization treatment.  
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Key Words: Chronic total occlusion; Elderly; Medical therapy

Generally, the diminished physical activity associated with aging may not allow elderly patients to increase their myocardial oxygen demand, which may induce symptoms of angina. In addition, patients of advanced age carry a higher burden of comorbid illness and more advanced coronary lesions; these findings may be related to the occurrence of complications during or after invasive therapies. Accordingly, in elderly patients, MT may confer advantages compared with an aggressive revascularization strategy. Because this hypothesis has not been fully evaluated, we sought to investigate the clinical outcomes of an MT strategy in elderly patients with CTO, as compared with those undergoing revascularization.
Methods

Study Population
Between March 2003 and February 2012, 2,024 consecutive patients were enrolled in the Samsung Medical Center CTO registry. Clinical, laboratory and outcome data were collected by a trained study coordinator using a standardized case report form and protocol. If necessary, additional information was documented by contacting the principal investigators and/or by review of hospital records. The Institutional Review Board at Samsung Medical Center approved the study protocol and waived the requirement for informed consent. The inclusion criteria for the registry were: (1) age ≥75 years, (2) at least one CTO detected on diagnostic coronary angiography and (3) symptomatic angina and/or a positive functional ischemia study. Exclusion criteria included: (1) previous CABG, (2) history of cardiogenic shock or cardiopulmonary resuscitation and (3) ST-segment elevation acute myocardial infarction (MI) during the preceding 48 h. Among the patients registered, 311 elderly patients were ultimately included in this analysis. Even the definition of “elderly” varies widely: we defined elderly as >75 years old, because most previous studies of PCI in elderly patients used the same criterion.9,10 The patient flow of the study is shown in Figure 1. Subjects were classified into the MT and revascularization groups according to the intention-to-treat approach.

Treatment Strategy
All patients received antiplatelet therapy with aspirin at a dose of 81–325 mg/day or clopidogrel 75 mg/day if aspirin intolerance was reported. All patients were taking one or more antianginal medications, including a long-acting β-blocker, calcium-channel blocker and isosorbide mononitrate, alone or in combination, as well as either an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker and lipid-lowering agents as standard secondary prevention. The dosage of all medications was maximized as allowed by heart rate, blood pressure and side effects in the absence of justifiable relative contraindications. Revascularization of CTOs was accomplished by CABG or PCI with a drug-eluting stent (DES). The revascularization strategy was selected based on both the patient’s and physician’s preferences. In the case of CABG for CTOs, arterial grafting with off-pump coronary artery bypass was the preferred technique. PCI was performed using contemporary techniques such as bilateral injections, a specialized stiff, hydrophilic wire with a tapered tip, microcatheters and a retrograde approach when possible. The decision to pursue invasive treatment, choice of access site and type of DES, use of intracoronary ultrasound and use of glycoprotein IIb/IIIa receptor inhibitors were all left to the operator’s discretion. All interventions and procedural anticoagulation were performed according to current standard guidelines. All patients received loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) before PCI unless they had previously received these antiplatelet medications. Aspirin treatment was continued indefinitely, but the duration of clopidogrel treatment was left to the discretion of the physician.

Definition and Outcomes
A CTO lesion was defined as the obstruction of a native coronary artery with a Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 with an estimated duration >3 months.3 Duration was estimated based on the interval from the last episode of acute coronary syndrome (ACS) or, in patients with no history of ACS, from the first episode of exertional angina consistent with the location of the occlusion or previous coronary angiography. Successful PCI was defined as final residual stenosis <20% of the vessel diameter, with TIMI flow grade ≥2 after revascularization, as assessed by visual estimation on angiography.

The primary outcome was cardiac death during follow-up. The secondary outcomes were MI, repeat revascularization and major adverse cardiac events (MACEs). Repeat revascularization was a composite of target vessel revascularization and non-target vessel revascularization treated with PCI or CABG. MACE was defined as a composite of cardiac death, MI and repeat revascularization. All deaths were considered to be of cardiac origin unless a definite non-cardiac cause could be established.14 MI was defined as recurrent symptoms with new ECG changes compatible with MI or cardiac markers at least twice the upper limit of normal.15 Perioperative or periprocedural enzyme elevation was not included in this definition of MI.

Statistical Analysis
Comparisons for continuous variables were made using the t-test or the Wilcoxon rank-sum test when applicable and results were presented as mean±standard deviation or medians with interquartile range (IQR). Differences between each group were evaluated using chi-squared or Fisher’s exact tests for categorical data. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. To retain a large sample size and maximize the study power while maintaining a balance in covariates between the 2 groups, we conducted rigorous adjustment for differences in baseline and lesion characteristics of patients using the weighted Cox proportional-hazards regression models with the inverse probability of treatment weighting (IPTW). According to this technique, weights for patients receiving MT were the inverse of 1 – the propensity score. The propensity scores were estimated without regard to outcomes, using multiple logistic-regression analysis. Model discrimination was assessed with c-statistics and model calibration was assessed with Hosmer-Lemeshow statistics. The results of IPTW were verified by those of propensity score-matching. The covariate balance achieved by matching was assessed by calculating the absolute standardized differences in covariates between the MT and revascularization groups. An absolute standardized difference of <10% for the measured covariate suggests appropriate balance between groups. In the propensity score-matched population, continuous variables were
the MT group and 158 in the revascularization group. In the revascularization group, 91 patients had successful PCI, 43 patients had CABG and 24 patients had a failed PCI; 35 patients were planned to undergo second-stage PCI and their median duration from initial coronary angiography to PCI was 3 (IQR 1–18) days. Also, the median duration from initial coronary angiography to CABG was 4 (IQR 2–6) days. The baseline characteristics of the study population are described in Table 1. Compared with patients in the revascularization group, those in the MT group were older and had a lower left ventricular ejection fraction (LVEF), more history of prior MI and peripheral artery disease than the revascularization group.

Results

Baseline and Procedural Characteristics
The 311 patients were divided into 2 groups: 153 patients in the MT group and 158 in the revascularization group. In the revascularization group, 91 patients had successful PCI, 43 patients had CABG and 24 patients had a failed PCI; 35 patients were planned to undergo second-stage PCI and their median duration from initial coronary angiography to PCI was 3 (IQR 1–18) days. Also, the median duration from initial coronary angiography to CABG was 4 (IQR 2–6) days. The baseline characteristics of the study population are described in Table 1. Compared with patients in the revascularization group, those in the MT group were older and had a lower left ventricular ejection fraction (LVEF), more history of prior MI and peripheral artery disease than the revascularization group.
lution, but a lower prevalence of ACS. After adjustment for the baseline characteristics with IPTW, there were no significant intergroup differences in the baseline covariates and propensity score-matching yielded a cohort that was well balanced for all baseline covariates. Moreover, after performing propensity score-matching for the entire population, a total of 106 matched pairs of patients were created. The c-statistic for the propensity score model was 0.751. There were no significant differences in baseline clinical characteristics between the MT and revascularization groups for the propensity-matched subjects. Lesion characteristics of both groups are shown in Table 2. The number of CTO in the left anterior descending artery was higher in the revascularization group than in the MT group. Otherwise, there were no significant differences in lesion characteristics, including CTO at the proximal to mid part, multiple CTOs and collateral grade, between the 2 groups. After adjustment with IPTW, we found no significant intergroup differences as for the baseline characteristics. Also, there were no significant differences in lesion characteristics between the 2 groups in the propensity score-matched population.

### Clinical Outcomes

The median follow-up duration was 34 (IQR 14–58) months in the MT group and 34 (IQR 15–57) months in the revascularization group. Table 3 shows the cumulative clinical outcomes of the 2 groups. After univariate analysis, the incidence of cardiac death in the MT group was higher than in the revascularization group (MT group vs. revascularization group: Cardiac death 30 (19.6) vs. 17 (10.8), HR 1.96 (1.08–3.55) vs. 1.43 (0.76–2.69), P = 0.027 vs. 0.27, Adjusted HR 1.26 (0.71–2.21) vs. 0.78).

### Table 3. Clinical Outcomes of Optimal Medical Therapy vs. Revascularization During Follow-up in 311 Elderly Patients With Coronary CTO

<table>
<thead>
<tr>
<th>Total population</th>
<th>Medical therapy</th>
<th>Revascularization</th>
<th>Unadjusted HR (95% CI)</th>
<th>P value</th>
<th>Multivariate analysis</th>
<th>IPTW</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Cardiac death</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>30 (19.6)</td>
<td>17 (10.8)</td>
<td>1.96 (1.08–3.55)</td>
<td>0.027</td>
<td>1.43 (0.76–2.69)</td>
<td>0.27</td>
<td>1.26 (0.71–2.21)</td>
<td>0.43</td>
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<td><strong>MI</strong></td>
<td></td>
<td></td>
<td>2.12 (0.63–7.05)</td>
<td>0.21</td>
<td>1.51 (0.41–5.66)</td>
<td>0.54</td>
<td>1.16 (0.39–3.54)</td>
<td>0.78</td>
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<tr>
<td><strong>Repeat revascularization</strong></td>
<td></td>
<td></td>
<td>1.09 (0.50–2.34)</td>
<td>0.84</td>
<td>0.85 (0.93–2.10)</td>
<td>0.85</td>
<td>1.06 (0.47–2.41)</td>
<td>0.89</td>
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<tr>
<td><strong>MACE</strong></td>
<td>40 (26.1)</td>
<td>29 (18.4)</td>
<td>1.50 (0.93–2.43)</td>
<td>0.09</td>
<td>1.08 (0.65–1.82)</td>
<td>0.76</td>
<td>1.14 (0.71–1.83)</td>
<td>0.60</td>
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</table>

Values are n (%). *Repeat revascularization included target lesion revascularization, target vessel revascularization and non-target vessel revascularization with CABG or PCI. **Covariates include age, history of PCI, history of MI, history of PAD, LVEF, ACS and CTO at LAD. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event. Other abbreviations as in Tables 1, 2.

Figure 2. Kaplan-Meier curves for the medical therapy group (red line) and revascularization group (blue line) in crude populations. Curves for (A) cardiac death, (B) myocardial infarction, (C) repeat revascularization and (D) major adverse cardiovascular event (MACE).
A certain proportion of CTO patients who are either asymptomatic or minimally symptomatic do not undergo diagnostic coronary angiography. As a result, the true prevalence of CTO in the general population remains unknown. CTO is more commonly seen in the older population, which frequently carries comorbidities such as peripheral artery disease, stroke and diabetes.\(^{16-18}\) In addition, the risk of periprocedural complications may be higher in elderly patients because of the more extensive coronary artery lesions, heavy calcification and tortuosity of vessels in this population.\(^{19,20}\)

As the number of elderly patients presenting for treatment of CTO continues to increase, guidance for the optimal treatment in elderly patients with CTO is needed. Several previous studies showed that relief of angina and quality of life were similar for elderly patients with chronic stable angina who were medically treated and those who underwent revascularization.\(^{21,22}\) The COURAGE trial showed that the addition of PCI to optimal MT was not a cost-effective initial management strategy for symptomatic, chronic coronary artery disease (CAD).\(^{23}\) A recent study found that CTO-PCI is cost-effective in patients

\[ \text{Values are n (%).} \]

<table>
<thead>
<tr>
<th>Propensity-matched population (n=106)</th>
<th>Medical therapy</th>
<th>Revascularization</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>20 (18.9)</td>
<td>14 (13.2)</td>
<td>1.52 (0.76–3.07)</td>
<td>0.24</td>
</tr>
<tr>
<td>MI</td>
<td>5 (4.7)</td>
<td>4 (3.8)</td>
<td>1.28 (0.34–4.85)</td>
<td>0.71</td>
</tr>
<tr>
<td>Repeat revascularization*</td>
<td>9 (8.5)</td>
<td>10 (9.4)</td>
<td>0.93 (0.37–2.28)</td>
<td>0.88</td>
</tr>
<tr>
<td>MACE</td>
<td>27 (25.5)</td>
<td>23 (21.7)</td>
<td>1.22 (0.69–2.16)</td>
<td>0.50</td>
</tr>
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</table>

\(*\text{Repeat revascularization included target lesion revascularization, target vessel revascularization and non-target vessel revascularization with CABG or PCI.} \)

Abbreviations as in Tables 1, 3.

**Discussion**

In the present study, we investigated the clinical outcomes of MT vs. revascularization strategy in elderly patients with CTO and showed that the 2 strategies have a comparable risk of long-term cardiac death.
with severe symptoms. However, many elderly patients may not present with severe symptoms owing to decreased physical activity and oxygen demand. Hence, physicians may prefer conservative therapy over invasive therapy for these patients in real world practice. In fact, a Canadian multicenter CTO registry showed that patients treated medically tended to be slightly older than those who underwent revascularization.

CTO revascularization by PCI or CABG is a very complex procedure. As a result, current guidelines for myocardial revascularization recommend that PCI for CTO should be restricted to operators with a success rate >80%. Coronary intervention in elderly CTO patients may be more difficult than in younger CTO patients because of lesion complexity and susceptibility to transient ischemia. Furthermore, elderly patients present a higher rate of complications, such as access site injury or additional transfusions, during and after the procedure. In the case of CABG, intraoperative or postoperative MI, low cardiac output syndrome, stroke, gastrointestinal complications, wound infection and renal failure occur more frequently in elderly patients after cardiac surgery and predict adverse outcomes. Accordingly, aggressive revascularization in elderly patients with CTO should be carefully determined under consideration of lesion characteristics, physiological age and physical activity.

Revascularization for CTO in elderly patients is being increasingly attempted and several previous studies have investigated the outcomes after PCI for CTO in such patients. However, most of those studies compared successful PCI and failed PCI. To the best of our knowledge, there has been no comparison between MT and revascularization therapy. Likewise, there is no widely accepted guideline or consensus on treating elderly CTO patients, as the benefit of PCI in this population is poorly understood. In this study, MT patients were high-risk subjects such as those of older age, with a history of MI and decreased LVEF. Although cardiac death was more frequent in the MT group than in the revascularization group by univariate analysis, this difference was no longer significant on multivariate analysis, adjusted Cox analysis by IPTW or propensity score-matching. A previous randomized comparison between MT and revascularization therapy. Likewise, there is no widely accepted guideline or consensus on treating elderly CTO patients, as the benefit of PCI in this population is poorly understood. In this study, MT patients were high-risk subjects such as those of older age, with a history of MI and decreased LVEF. Although cardiac death was more frequent in the MT group than in the revascularization group by univariate analysis, this difference was no longer significant on multivariate analysis, adjusted Cox analysis by IPTW or propensity score-matching. A previous randomized trial, conducted in elderly patients with chronic symptomatic CAD, showed no difference in 1-year clinical outcomes between MT and revascularization, including symptoms, quality of life, death or non-fatal MI. Those findings are corroborated by our study of patients with CTO.

Study Limitations
First, it was not a randomized trial: the selection of treatment was influenced by the patient’s characteristics and the patient’s and physician’s preferences. Second, the number of subjects was relatively small as the study targeted elderly patients only. The study population was further decreased to conduct propensity score-matching. Third, we did not routinely evaluate the amount of viable myocardium or ischemia in the study patients using functional ischemia testing. Despite these limitations, our study provided data from a long-term follow-up, utilized strict approaches to adjusting for several contributing factors using the IPTW methods and propensity matching, and made a direct comparison of MT and revascularization therapy, which may benefit future investigations.

Conclusions
In the treatment of elderly CTO patients, MT had a similar rate of cardiac death in long-term follow-up as revascularization therapy. Larger randomized controlled trials are needed to support this finding.

References


Supplementary Files
Supplementary File 1
Table S1. Clinical outcomes of PCI at LAD to non-LAD in entire population of elderly patients with coronary CTO
Table S2. Clinical outcomes of elderly patients with coronary CTO treated with PCI then undergone CABG
Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-15-0041