Impact of Residual Chronic Total Occlusion of Right Coronary Artery on the Long-term Outcome in Patients Treated for Unprotected Left Main Disease

The Milan and New-Tokyo Registry

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Background—The presence of chronic total occlusion of the right coronary artery (CTO-RCA) in patients undergoing percutaneous interventions for unprotected left main (ULM) disease may affect the prognosis. In this study, we evaluated the immediate results and follow-up of patients with ULM-percutaneous interventions and with or without associated CTO-RCA.

Methods and Results—Between March 2002 and December 2008, a total of 568 consecutive patients with ULM stenosis treated with drug-eluting stent were included in this analysis. The mean EuroScore and SYNTAX scores were 4.05±2.62 and 28.12±10.82, respectively. Of these, 522 had ULM lesions without residual CTO-RCA (493 ULM without CTO-RCA+29 ULM with treated CTO-RCA), and 46 patients had residual CTO-RCA. At 1466 days (interquartile range, 1150–1917) follow-up, the cardiac-death occurred in 41 patients (7.2%). Cardiac-death was more frequently observed in patients with ULM and residual CTO-RCA as compared with those without residual CTO-RCA (adjusted hazard ratios, 2.163 [95% confidence interval, 1.018–4.597]; \(P=0.045\)). However, target lesion revascularization occurred less frequently in patients with residual CTO-RCA (adjusted hazard ratios, 0.321 [95% confidence interval, 0.13–0.794]; \(P=0.014\)), resulting in the similar major adverse cardiovascular events rates between the 2 groups. When we analyzed patients with concomitant ULM and CTO-RCA, cardiac-death was significantly higher in patients with residual as compared with treated CTO-RCA (log-rank \(P=0.01\)) despite no difference in baseline characteristics.

Conclusions—Cardiac-death occurred more frequently in patients with residual CTO-RCA as compared with those without residual CTO-RCA. These findings suggest that recanalization of CTO-RCA has significant impact on the long-term cardiac-mortality in patients undergoing ULM-percutaneous interventions probably by offering reserve coronary circulation, if in-stent restenosis were to occur in the treated left main. (Circ Cardiovasc Interv. 2013;6:154-160.)

Key Words: chronic total coronary occlusion ■ drug-eluting stent ■ left main coronary artery ■ right coronary artery

With continual improvements in stent technology and adjunctive pharmacotherapy, we have supportive evidence regarding percutaneous coronary intervention (PCI) and drug-eluting stent (DES) implantation in selected unprotected left main (ULM) lesions involving ostium/body or distal bifurcation with low-to-moderate SYNTAX scores.\(^1\)\(^\text{-}\)\(^4\) Conversely, in patients with SYNTAX score \(>32\), coronary artery bypass grafting (CABG) is recommended.\(^5\) The presence of chronic total occlusion of the right coronary artery (CTO-RCA) contributes to the generation of a high SYNTAX score in patients with ULM stenosis. There is scarcity of data on the impact of residual CTO-RCA in patients undergoing PCI for ULM, and we aim to study this aspect in our cohort of patients.

Methods

Between April 2002 and December 2008, a retrospective cohort analysis was performed in 568 consecutive patients with de novo ULM disease after sirolimus-eluting stent (Cypher, Cordis Corporation, Johnson & Johnson, Warren, NJ) or paclitaxel-eluting stent (Taxus, Cordis Corporation, Warren, NJ).
WHAT IS KNOWN

• The presence of chronic total occlusion of right coronary artery (CTO-RCA) may be associated with a worse clinical outcome in patients undergoing unprotected left main- percutaneous interventions than with similar comorbidities but with successful recanalization of CTO-RCA.

• There is little data available regarding the impact of successful recanalization for CTO-RCA on long-term mortality in patients with unprotected left main.

WHAT THE STUDY ADDS

• Cardiac-death occurred more frequently in patients with untreated CTO-RCA as compared with those with successfully recanalized CTO-RCA despite similar comorbidities, whereas in-stent restenosis occurred less frequently in patients with untreated CTO-RCA.

• An occluded RCA has negative impact on the long-term cardiac-mortality in patients undergoing unprotected left main-percutaneous interventions.

Boston Scientific, Natick, MA) implantation in 3 high volume centers (San Raffaele Scientific Institute, Milan, Italy, EMO-GVM Centro Cuore Columbus, Milan, Italy and New-Tokyo Hospital, Chiba, Japan). Study population is described in Figure 1. The decision to perform PCI rather than CABG was taken in the presence of suitable anatomy and lesion characteristics for PCI: absence of any contraindications to at least 6 months of dual antiplatelet therapy; and one of the following conditions: (1) high-surgical risk defined as Euroscore ≥ 6 (European System for Cardiac Operative Risk evaluation) and (2) patient refusal to undergo CABG. All patients were carefully informed about the alternative treatment options and the PCI-related risks before being asked to give written informed consent to the procedure. PCI rather than CABG was taken in the presence of suitable anatomy and lesion characteristics for PCI: absence of any contraindications to at least 6 months of dual antiplatelet therapy; and one of the following conditions: (1) high-surgical risk defined as Euroscore ≥ 6 (European System for Cardiac Operative Risk evaluation) and (2) patient refusal to undergo CABG. All patients were carefully informed about the alternative treatment options and the PCI-related risks before being asked to give written informed consent to the procedure.

ULM disease was defined as a stenosis of at least 50% involving the ostium, body, or distal segment of the left main with involvement of the left anterior descending, the left circumflex, or both. ULM lesions were divided into 2 groups: ostium and body (nonbifurcation lesions) and distal bifurcation (unprotected distal left main disease). True bifurcation lesion was defined as medina class 1-1-1, 1-0-1, 0-1-1 by 2 independent physicians.10 CTO-RCA was defined as complete occlusion with thrombolysis in myocardial infarction 0 flow lasting at least 3 months, regardless of the occluded location in dominant RCA. Patients with CTO-RCA were divided into 2 groups: ULM with treated CTO-RCA, when the occlusion was successfully treated by PCI either before or after ULM-PCI, and ULM with residual CTO-RCA, when PCI was not attempted or failed. ULM without initial CTO-RCA and ULM with treated CTO-RCA were included under a single group (ULM without residual CTO-RCA).

The antiplatelet regimens were low-dose aspirin, which was recommended indefinitely, and a thienopyridine (200–250 mg of ticlopidine bid or 75 mg of clopidogrel daily) for a minimum of 6 months after PCI. Clinical data were collected by hospital visit or telephone contact at 6 month intervals. Angiographic follow-up was scheduled between 3 and 12 months or earlier if noninvasive evaluation or clinical presentation suggested the presence of ischemia.

Study End Points

The study end point was cardiac mortality during follow-up period. The primary end point was cardiac mortality during follow-up period. Death was considered cardiac in origin unless obvious noncardiac causes could be identified. Secondary end points were all-cause mortality, target lesion revascularization (TLR), and major adverse cardiovascular events (MACE), which were defined as cardiac-death, myocardial infarction (MI), or TLR (defined as repeat PCI or CABG for significant restenosis in the previously stented segment or in the adjacent 5 mm). Periprocedural MI was defined as the presence of pathological and new Q waves on an ECG, or an increase in creatine kinase-myocardial band level to >3× the upper limit of the normal range. Spontaneous MI and stent thrombosis was defined according to the Academic Research Consortium definitions.11 Chronic kidney disease was defined by an estimated glomerular filtration rate (e-GFR) <60 mL/min per 1.73 m². Severe chronic kidney disease was defined by e-GFR <15 mL/min per 1.73 m².12 Clinical risk was defined according to EuroScore (low-risk ≤2, intermediate-risk 3–5, and high-risk ≥6)13–15 and SYNTAX Score (low 0–22, intermediate 23–32, and high ≥33).13

Statistical Analysis

Continuous variables were expressed as mean±SD. Comparisons of clinical, echocardiographic, and angiographic or procedure-related characteristics of patients were performed by means of Student t test or Wilcoxon rank-sum test (continuous variables), or χ² (categorical)
and according to residual CTO-RCA. Comparisons of event-free survival (Kaplan–Meier curves) were performed with the log-rank test. Univariate Cox regression analyses were used to identify correlation between cardiac-death and all covariates in Tables 1 and 2. Cox regression analysis using purposeful selection of covariates was performed to determine the independent predictors of cardiac-death during follow-up period after ULM-PCI using predictors associated with cardiac-death ($P<0.1$) and those judged to be of clinical importance from previous published literature. To avoid overfitting, the number of independent variables entered into the final multivariable model was limited to a maximum of 1 for every 8 events. The results are reported as adjusted hazard ratios (HR) with associated 95% confidence interval (CI). A propensity score analysis was performed using a logistic regression model from which the probability for a residual CTO-RCA was calculated for each patient. Model discrimination was assessed with the c-statistic and goodness-of-fit with Hosmer and Lemeshow test. All analyses were conducted using SPSS software version 18.0, and all reported $P$ values are 2-sided. Values of $P<0.05$ were regarded as statistically significant.

## Results

### Overall Population

During the study period, 568 consecutive patients with de novo ULM disease were treated with first generation DES (452 sirolimus-eluting stent or 116 paclitaxel-eluting stent). Baseline clinical, lesion, and procedural characteristics of patients with ULM are shown in Tables 1 and 2. The mean age was 67.8±10.5 years, 78.5% were men, and diabetes mellitus (DM) was present in 34.0% and chronic kidney disease in 44.8% of the patients. In terms of risk stratification, the mean standard EuroSCORE was 4.1±2.6, and SYNTAX Score was 28.1±10.8. A total of 26.9% had a EuroSCORE>6, and 30.3% had a SYNTAX score in the third tertile (>33). Furthermore, 40.0% had ULM disease with 3-vessel disease, and 88.4% had distal bifurcation disease. At baseline, the RCA was patent in 493 patients (86.8%). The residual 75 patients (13.2%) had ULM with concomitant CTO-RCA; 29 patients (38.6%) were successfully treated, and 46 patients (61.4%) were left untreated or failed an attempt to open CTO-RCA. Patients with residual CTO-RCA had more severe comorbidities as compared with ULM without residual CTO-RCA (previous MI, chronic kidney disease, low-ejection fraction) and more severe DIAB (44.8%) and SYNTAX score ($P<0.1$) and those judged to be of clinical importance from previous published literature.

### Table 1. Baseline Clinical Characteristics of Patients Treated for ULM According to the Residual CTO-RCA

<table>
<thead>
<tr>
<th>Patients: n</th>
<th>Overall ULM</th>
<th>ULM Without Residual CTO RCA</th>
<th>ULM With Residual CTO RCA N=46</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.78±10.46</td>
<td>68.00±10.33</td>
<td>65.28±11.60</td>
<td>0.09</td>
</tr>
<tr>
<td>Male sex</td>
<td>446 (78.5)</td>
<td>406 (77.8)</td>
<td>40 (87.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous MI</td>
<td>220 (38.7)</td>
<td>195 (37.4)</td>
<td>25 (54.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>25 (4.1)</td>
<td>25 (4.8)</td>
<td>4 (8.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>318 (56.6)</td>
<td>299 (57.3)</td>
<td>19 (41.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>193 (34.0)</td>
<td>178 (34.2)</td>
<td>15 (32.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>433 (76.2)</td>
<td>404 (77.4)</td>
<td>29 (63.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>373 (65.8)</td>
<td>337 (64.7)</td>
<td>36 (78.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>CKD (estimated GFR&lt;60)</td>
<td>254 (44.8)</td>
<td>226 (43.4)</td>
<td>28 (60.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Severe CKD (estimated GFR&lt;15)</td>
<td>23 (4.1)</td>
<td>20 (3.8)</td>
<td>3 (6.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>56 (10.3)</td>
<td>48 (9.6)</td>
<td>8 (17.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>55.96±9.93</td>
<td>56.68±9.47</td>
<td>47.78±11.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction &lt;55%</td>
<td>35 (6.2)</td>
<td>26 (5.0)</td>
<td>9 (19.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>EuroScore (standard)</td>
<td>4.05±2.62</td>
<td>3.99±2.56</td>
<td>4.76±3.22</td>
<td>0.06</td>
</tr>
<tr>
<td>EuroScore&gt;6</td>
<td>153 (26.9)</td>
<td>137 (26.2)</td>
<td>16 (34.8)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Data are presented as percentages and absolute numbers or means±SD, unless otherwise specified. CKD indicates chronic kidney disease; CTO-RCA, chronic total occlusion of right coronary artery; estimated GFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; and ULM, unprotected left main.

### Table 2. Baseline Angiographic and Procedural Characteristics of Patients Treated for ULM According to Residual CTO-RCA

<table>
<thead>
<tr>
<th>Patients: n</th>
<th>Overall ULM</th>
<th>ULM Without Residual CTO RCA N=522</th>
<th>ULM With Residual CTO RCA N=46</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal bifurcation ULM</td>
<td>502 (88.4)</td>
<td>461 (88.5)</td>
<td>41 (89.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>True-bifurcation media</td>
<td>330 (58.1)</td>
<td>296 (56.7)</td>
<td>34 (73.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Initial CTO LAD</td>
<td>34 (6.0)</td>
<td>28 (5.4)</td>
<td>6 (13.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Untreated CTO LAD</td>
<td>9 (1.6)</td>
<td>5 (1.0)</td>
<td>4 (8.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Initial CTO LCx</td>
<td>31 (5.5)</td>
<td>26 (5.0)</td>
<td>5 (10.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Untreated CTO LCx</td>
<td>18 (3.2)</td>
<td>15 (2.9)</td>
<td>3 (6.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>ULM+3 VD</td>
<td>227 (40.0)</td>
<td>201 (38.5)</td>
<td>26 (56.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Syntax score</td>
<td>28.12±10.82</td>
<td>27.62±10.76</td>
<td>33.78±10.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Syntax&gt;33</td>
<td>172 (30.3)</td>
<td>148 (28.4)</td>
<td>24 (52.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>IABP</td>
<td>84 (15.2)</td>
<td>69 (13.6)</td>
<td>15 (32.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>IVUS</td>
<td>297 (52.3)</td>
<td>279 (53.4)</td>
<td>18 (39.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Rotational atherectomy</td>
<td>35 (6.2)</td>
<td>35 (6.8)</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Calcification</td>
<td>333 (58.6)</td>
<td>306 (59.0)</td>
<td>25 (54.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>SES</td>
<td>452 (79.6)</td>
<td>422 (80.8)</td>
<td>30 (65.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>PES</td>
<td>116 (20.4)</td>
<td>100 (19.2)</td>
<td>16 (34.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Bif-2 stent</td>
<td>199 (35.0)</td>
<td>180 (34.5)</td>
<td>19 (41.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Provisional T-stent</td>
<td>25 (4.4)</td>
<td>21 (4.0)</td>
<td>4 (8.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>SKS or V-stent</td>
<td>24 (4.2)</td>
<td>17 (3.3)</td>
<td>7 (15.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Crush</td>
<td>47 (8.3)</td>
<td>44 (8.4)</td>
<td>3 (6.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Mini-Crush</td>
<td>64 (11.2)</td>
<td>61 (11.7)</td>
<td>3 (6.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Culotte</td>
<td>28 (4.9)</td>
<td>28 (5.4)</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Triple stenting</td>
<td>11 (1.9)</td>
<td>9 (1.7)</td>
<td>2 (4.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Final kissing balloon</td>
<td>419 (74.2)</td>
<td>392 (75.5)</td>
<td>27 (58.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>No. of stents/patients</td>
<td>1.37±0.53</td>
<td>1.36±0.52</td>
<td>1.47±0.58</td>
<td>0.20</td>
</tr>
<tr>
<td>Total stent length/ patient, mm</td>
<td>27.78±14.40</td>
<td>27.28±14.02</td>
<td>33.43±17.83</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum stent size</td>
<td>3.39±0.28</td>
<td>3.38±0.28</td>
<td>3.45±0.26</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data are presented as percentages and absolute numbers or means±SD, unless otherwise specified. Bif-2 stent indicates bifurcation 2 stent technique; CTO-RCA, chronic total occlusion of right coronary artery; IABP, intra-aorta balloon pumping; IVUS, intra vascular ultra sound; LAD, left anterior descending artery; LCx, left circumflex artery; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SKS, simultaneous kissing stent; 3 VD, 3 vessel disease; and ULM, unprotected left main.
complicated lesions (more CTO of left anterior descending, high SYNTAX, and a higher usage of intra-aortic balloon pump; Tables 1 and 2).

During hospitalization, 2 patients died (one had cerebral bleeding and the other had sudden cardiac arrest at 4 days after PCI), and 19 patients (3.3%) had a non–Q-wave MI.

The median clinical follow-up was 1466 days (interquartile range, 1150–1917). Dual antiplatelet therapy was prescribed for at least 6 months after DES implantation, and 93.5% of patients were still on dual antiplatelet therapy at 12 months.

Overall, 83 patients (14.6%) died, and cardiac-death occurred in 41 patients (7.2%). Cardiac-death was more frequently observed in patients with residual CTO-RCA than those without residual CTO-RCA (adjusted HR, 2.163 [95% CI, 1.018–4.597]; \( P=0.045 \)). Furthermore, cardiac-death and MI occurred in 48 patients (8.2%) and were more frequently observed in patients with residual CTO-RCA than those without residual CTO-RCA.

MACE occurred in 155 patients (27.3%), notably the occurrence of MACE was quite similar between the 2 groups. The overall TLR was performed in 125 patients (22.0%). Interestingly, TLR occurred less frequently in patients with residual CTO-RCA (adjusted HR, 0.321 [95% CI, 0.13–0.794]; \( P=0.014 \)).

Definite ST in LM was observed in 8 patients (1.4%) and probable ST in 5 patients (0.9%). Clinical outcome is summarized in Table 3, and adjusted freedom from cardiac-death and TLR are illustrated in Figure 2.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients With ULM and No Residual CTO-RCA (n=522)</th>
<th>Patients With ULM and Residual CTO-RCA (n=46)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death (absolute number)</td>
<td>68</td>
<td>15</td>
<td>0.003</td>
</tr>
<tr>
<td>1-y, % (n=538)</td>
<td>23.8±0.8</td>
<td>4.3±3.0</td>
<td></td>
</tr>
<tr>
<td>3-y, % (n=477)</td>
<td>7.8±1.2</td>
<td>17.6±5.7</td>
<td></td>
</tr>
<tr>
<td>5-y, % (n=157)</td>
<td>15.1±1.9</td>
<td>30.7±7.3</td>
<td></td>
</tr>
<tr>
<td>Cardiac-death (absolute number)</td>
<td>30</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-y, % (n=538)</td>
<td>2.3±0.7</td>
<td>4.3±3.0</td>
<td></td>
</tr>
<tr>
<td>3-y, % (n=477)</td>
<td>4.1±0.9</td>
<td>17.6±5.7</td>
<td></td>
</tr>
<tr>
<td>5-y, % (n=157)</td>
<td>6.6±1.2</td>
<td>22.7±6.4</td>
<td></td>
</tr>
<tr>
<td>TLR (absolute number)</td>
<td>120</td>
<td>5</td>
<td>0.048</td>
</tr>
<tr>
<td>1-y, % (n=456)</td>
<td>17.0±1.7</td>
<td>4.4±3.1</td>
<td></td>
</tr>
<tr>
<td>3-y, % (n=382)</td>
<td>21.7±1.8</td>
<td>7.2±4.0</td>
<td></td>
</tr>
<tr>
<td>5-y, % (n=123)</td>
<td>24.6±2.1</td>
<td>11.4±5.6</td>
<td></td>
</tr>
<tr>
<td>3-y MI</td>
<td>2.0±0.1</td>
<td>4.4±3.1</td>
<td>0.709</td>
</tr>
<tr>
<td>3-y cardiac-death+MI, %</td>
<td>4.7±0.9</td>
<td>17.6±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3-y MACE, % (cardiac-death+MI+TLR)</td>
<td>24.2±1.9</td>
<td>24.2±6.4</td>
<td>0.878</td>
</tr>
</tbody>
</table>

CTO-RCA indicates chronic total occlusion of right coronary artery; MACE, major adverse cardiovascular event; MI, myocardial infarction; TLR, target lesion revascularization; and ULM, unprotected left main.

Outcome rates were derived from Kaplan–Meier curves.

Patients With Treated Versus Residual CTO-RCA

Patients were further analyzed according to treatment of a concomitant CTO-RCA and divided in treated (n=29) versus residual (n=46) CTO-RCA. No differences were observed between the 2 groups in baseline clinical and lesion characteristics (Tables 4 and 5) except for more previous PCI in

![Figure 2](http://circinterventions.ahajournals.org/)

**Figure 2.** Adjusted Cumulative events according to residual chronic total occlusion of right coronary artery (CTO-RCA) in all unprotected left main. **A**, Cardiac-death. **B**, Target lesion revascularization (TLR). FU indicates follow-up; LCL, lower confidence limit; UCL, upper confidence limit.
The main findings of our study are the following:

1. Patients with ULM without residual CTO-RCA had a lower cardiac-mortality compared with those with ULM with residual CTO-RCA.
2. Among patients with ULM and initial CTO-RCA, those who had successfully treated CTO-RCA had lower cardiac-mortality than patients who had persistence of CTO-RCA.
3. The need for TLR was higher among patients with ULM and open RCA versus patients with residual CTO-RCA.
4. The independent predictors of cardiac-death were e-GFR<60, DM, EuroScore, residual CTO-RCA, chronic total occlusion of right coronary artery; estimated GFR, estimated-glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; and ULM, unprotected left main.

Table 4. Baseline Clinical Characteristics of Patients Treated for ULM Disease With Initial CTO-RCA According to Recanalization of the CTO

<table>
<thead>
<tr>
<th>Patients: n</th>
<th>ULM With Initial CTO-RCA N=75</th>
<th>Successfully Treated CTO-RCA N=29</th>
<th>Residual CTO RCA N=46</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.57±11.70</td>
<td>63.45±11.96</td>
<td>65.28±11.60</td>
<td>0.51</td>
</tr>
<tr>
<td>Male sex</td>
<td>64 (85.3)</td>
<td>24 (82.8)</td>
<td>40 (87.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Previous MI</td>
<td>43 (57.3)</td>
<td>18 (62.1)</td>
<td>25 (54.3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>8 (10.7)</td>
<td>4 (13.8)</td>
<td>4 (8.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>40 (53.3)</td>
<td>21 (72.4)</td>
<td>19 (41.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (33.3)</td>
<td>10 (34.5)</td>
<td>15 (32.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (70.7)</td>
<td>24 (82.8)</td>
<td>29 (63.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>61 (81.3)</td>
<td>25 (89.7)</td>
<td>36 (78.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>CKD (estimated GFR&lt;60)</td>
<td>44 (58.7)</td>
<td>16 (55.2)</td>
<td>28 (60.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Severe CKD (estimated GFR&lt;15)</td>
<td>3 (4.0)</td>
<td>0</td>
<td>3 (6.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>12 (16.0)</td>
<td>4 (13.8)</td>
<td>8 (17.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>49.31±11.41</td>
<td>51.72±11.21</td>
<td>47.78±11.39</td>
<td>0.15</td>
</tr>
<tr>
<td>Ejection fraction &lt;35%</td>
<td>13 (17.3)</td>
<td>4 (13.8)</td>
<td>9 (19.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>EuroScore (standard)</td>
<td>4.61±2.97</td>
<td>4.38±2.57</td>
<td>4.76±3.22</td>
<td>0.97</td>
</tr>
<tr>
<td>EuroScore&gt;6</td>
<td>27 (36.0)</td>
<td>11 (37.9)</td>
<td>16 (34.8)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Data are presented as percentages and absolute numbers or means±SD, unless otherwise specified. CTO-RCA indicates chronic total occlusion of right coronary artery; estimated GFR, estimated-glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; and ULM, unprotected left main.

Predictors of Cardiac-Death

A P<0.1 in univariate analysis was the criterion used for inclusion in the final model. Adjusted covariates included e-GFR<60, DM, EuroScore, residual CTO-RCA, ejection fraction, untreated CTO-left anterior descending, intra-aorta balloon pumping, 3-vessel disease, calcification, true bifurcation, and male sex. On final Cox regression model, the independent predictors of cardiac-death during follow-up period were e-GFR<60 (HR, 3.468 [95% CI, 1.475–8.156]; P=0.004), DM (HR, 2.319 [95% CI, 1.224–4.392]; P=0.010), high EuroScore (HR, 1.152 [95% CI, 1.023–1.297]; P=0.020), low EF (5%; HR, 0.863 [95% CI, 0.747–0.996]; P=0.044), and residual CTO-RCA (HR, 2.163; [95% CI, 1.018–4.597]; P=0.045; Table 5). Multivariable analysis was also performed using the propensity score and residual CTO-RCA as covariates. The e-statistic of the regression model of the propensity score was 0.822 ( Hosmer and Lemeshow goodness-of-fit test, P=0.556). After adjusting for the propensity score, residual CTO-RCA remained significantly related to the risk of cardiac-death (HR, 2.412 [95% CI, 1.082–5.374]; P=0.031).

Table 5. Baseline Angiographic and Procedural Characteristics of Patients Treated for ULM Disease With Initial CTO-RCA According to Recanalization of the CTO

<table>
<thead>
<tr>
<th>Patients: n</th>
<th>ULM With Initial CTO-RCA N=75</th>
<th>Successfully Treated CTO-RCA N=29</th>
<th>Residual CTO RCA N=46</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal bifurcation</td>
<td>65 (86.7)</td>
<td>24 (82.8)</td>
<td>41 (89.1)</td>
<td>0.50</td>
</tr>
<tr>
<td>True-bifurcation</td>
<td>50 (67.6)</td>
<td>16 (57.1)</td>
<td>34 (73.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Syntax score</td>
<td>33.78±10.93</td>
<td>33.32±10.93</td>
<td>33.43±10.23</td>
<td>0.17</td>
</tr>
<tr>
<td>Syntax≥33</td>
<td>36 (48.0)</td>
<td>12 (41.4)</td>
<td>24 (52.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>IABP</td>
<td>23 (30.7)</td>
<td>8 (27.6)</td>
<td>15 (32.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>IVUS</td>
<td>30 (40.0)</td>
<td>12 (41.4)</td>
<td>18 (39.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Rotational atherectomy</td>
<td>2 (2.7)</td>
<td>0</td>
<td>2 (4.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Total stent length/ patient, mm</td>
<td>29.51±16.31</td>
<td>23.28±12.52</td>
<td>33.43±17.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum stent size</td>
<td>3.45±0.27</td>
<td>3.45±0.28</td>
<td>3.45±0.26</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Data are presented as percentages and absolute numbers or means±SD, unless otherwise specified. CTO-RCA indicates chronic total occlusion of right coronary artery; IABP, intra-aorta balloon pumping; IVUS, intra vascular ultra sound; LAD, left anterior descending artery; LCx, left circumflex artery; 3 VD, 3 vessel disease; and ULM, unprotected left main.

Discussion

The main findings of our study are the following:

1. Patients with ULM without residual CTO-RCA had a lower cardiac-mortality compared with those with ULM with residual CTO-RCA.
2. Among patients with ULM and initial CTO-RCA, those who had successfully treated CTO-RCA had lower cardiac-mortality than patients who had persistence of CTO-RCA.
3. The need for TLR was higher among patients with ULM and open RCA versus patients with residual CTO-RCA.
4. The independent predictors of cardiac-death were e-GFR<60, DM, high EuroScore, low EF, and residual CTO-RCA.

Patients with ULM and high SYNTAX tertile treated with PCI have been noted to have increased major adverse cardiovascular and cerebrovascular event as compared with patients treated with CABG.9 In addition, at 4 years, higher mortality
was observed in patients treated with PCI. The presence of CTO-RCA is an important determinant to generate a high SYNTAX score especially in patients with ULM. To our knowledge, there is only 1 study that has specifically addressed the impact of CTO-RCA recanalization in patients with ULM treated with PCI using DES. A previous study reported that in patients with ULM PCI and CTO-RCA, clinical and lesion characteristics were less favorable compared with the patients with no CTO-RCA, and consequently, their cardiac mortality at 18 months is higher.17 In our study, a larger patient population was analyzed at a longer follow-up period (median 1466 days). When we specifically evaluated the impact of successful recanalization of CTO-RCA in ULM PCI, the presence of residual CTO-RCA was significantly associated with higher restenosis or disease progression occurred in left system. Furthermore, a previous report by Mehran et al18 from a registry of 1791 patients exhibited that the presence of an untreated CTO is an independent predictor of mortality. One could argue that the survival benefit after successful recanalization of a CTO might be limited to certain subgroups. This was demonstrated by Safley et al19 who reported a significant benefit in survival after successful PCI of a CTO in the left anterior descending, but not in the left circumflex or RCA. In the context of ULM-PCI, recanalization of CTO-RCA is important to guarantee collateral circulation and provide reserve, if ULM restenosis were to occur.

In conclusion, our data might suggest that it may be advisable to recanalize a CTO-RCA before embarking ULM-PCI. However, if CTO-RCA cannot be recanalized successfully, such patients might be better served with surgical revascularization to obtain better long-term results.

**Limitations**

The main limitation of this study is the small cohort of patients and the lack of randomization. The study included a cohort of patients treated with first generation DES without a control epicardial vessel, such as RCA, in the context of treated ULM that could possibly protect from fatal events if an aggressive restenosis or disease progression occurred in left system.

Considering that majority of patients with ULM lesions and residual CTO-RCA had true bifurcation and severe comorbidities, we expected higher rates of restenosis. However, at 3 years, in the patients who had residual CTO-RCA, TLR occurred only in 7.2% patients as compared with 21.5% in patients with no residual CTO-RCA. The most likely explanations for this observation are the following: (1) higher incidence of cardiac-death, (2) more advanced disease prompting operators not to intervene, and (3) variability attributable to a small number of patients. On the contrary, sudden cardiac-death occurred only in 7.2% patients as compared with 21.5% in patients treated with PCI. The presence of residual CTO-RCA is significant associated with higher cardiac-mortality when compared with the patients with ULM and no residual CTO-RCA.

The occurrence of MACE was similar between the 2 groups. Considering that majority of patients with ULM lesions and residual CTO-RCA had true bifurcation and severe comorbidities, we expected higher rates of restenosis. However, at 3 years, in the patients who had residual CTO-RCA, TLR occurred only in 7.2% patients as compared with 21.5% in patients with no residual CTO-RCA. The most likely explanations for this observation are the following: (1) higher incidence of cardiac-death, (2) more advanced disease prompting operators not to intervene, and (3) variability attributable to a small number of patients. On the contrary, sudden cardiac-death occurred only in 7.2% patients as compared with 21.5% in patients who had treated CTO-RCA. Therefore, we cannot exclude the influence of patent major

### Table 6. Clinical Outcome of Patients With Concomitant ULM and CTO-RCA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ULM With Successfully Treated</th>
<th>CTO-RCA N=29</th>
<th>CTO RA N=46</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>2</td>
<td>15</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>1 y, % (n=71)</td>
<td>0</td>
<td>4.3±3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 y, % (n=60)</td>
<td>4.0±3.9</td>
<td>17.6±5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 y, % (n=26)</td>
<td>8.6±5.8</td>
<td>30.7±7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac-death</td>
<td>0</td>
<td>11</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>1 y, % (n=71)</td>
<td>0</td>
<td>4.3±3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 y, % (n=60)</td>
<td>0</td>
<td>17.6±5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 y, % (n=26)</td>
<td>0</td>
<td>22.7±6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>5</td>
<td>5</td>
<td>0.275</td>
<td></td>
</tr>
<tr>
<td>1 y, % (n=69)</td>
<td>3.7±3.6</td>
<td>4.4±3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 y, % (n=58)</td>
<td>11.1±6.0</td>
<td>7.2±4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 y, % (n=21)</td>
<td>20.6±8.4</td>
<td>11.4±5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 y MI</td>
<td>0</td>
<td>4.4±3.1</td>
<td>0.262</td>
<td></td>
</tr>
<tr>
<td>3-y cardiac-death + MI</td>
<td>0</td>
<td>17.6±5.7</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>3-y MACE (cardiac death +MI+TLR)</td>
<td>11.1±6.0</td>
<td>22.0±6.1</td>
<td>0.322</td>
<td></td>
</tr>
</tbody>
</table>

CTO-RCA indicates chronic total occlusion of right coronary artery; MACE, major adverse cardiovascular event; MI, myocardial infarction; TLR, target lesion revascularization; and ULM, unprotected left main.

Outcome rates were derived from Kaplan–Meier curves.

### Table 7. Predictors of Cardiac-Death During Follow-up Period (n=41) in Patients Treated With PCI for ULM

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable Hazard Ratio (Confidence Interval)</th>
<th>P Value</th>
<th>Cox Regression Adjusted Hazard Ratio (Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated GFR&lt;60</td>
<td>6.261 (2.775–14.126)</td>
<td>&lt;0.001</td>
<td>3.468 (1.475–8.156)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.328 (1.774–6.242)</td>
<td>&lt;0.001</td>
<td>2.319 (1.224–4.392)</td>
<td>0.010</td>
</tr>
<tr>
<td>EuroScore</td>
<td>1.335 (1.208–1.475)</td>
<td>&lt;0.001</td>
<td>1.152 (1.023–1.297)</td>
<td>0.020</td>
</tr>
<tr>
<td>Ejection fraction (5%)</td>
<td>0.726 (0.641–0.819)</td>
<td>&lt;0.001</td>
<td>0.863 (0.747–0.996)</td>
<td>0.044</td>
</tr>
<tr>
<td>Residual CTO-LAD</td>
<td>4.007 (2.006–8.004)</td>
<td>&lt;0.001</td>
<td>2.163 (1.018–4.597)</td>
<td>0.045</td>
</tr>
<tr>
<td>Untreated CTO-LAD</td>
<td>5.506 (1.694–17.899)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IABP</td>
<td>2.645 (1.370–5.107)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>2.062 (1.113–3.822)</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calciumization</td>
<td>2.341 (1.111–4.932)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True-bifurcation</td>
<td>2.013 (1.009–4.007)</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.531 (0.279–1.013)</td>
<td>0.055</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CTO-RCA indicates chronic total occlusion of right coronary artery; estimated GFR, estimated-glomerular filtration rate; IABP, intra-aorta balloon pumping; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; and ULM, unprotected left main.
CABG arm. Therefore, this is a major limitation while interpreting the results of the study. To clarify these results, further studies (randomized control trial, meta-analysis, or multicenter registry dedicated to the ULM disease and CTO-RCA) with more patient numbers, longer follow-up, and preferably considering patients treated with second generation DES would be ideal.

Conclusions

After PCI of ULM, cardiac-death occurred more frequently in patients with residual CTO-RCA, whereas no cardiac-death occurred in patients without residual CTO-RCA. These findings may suggest that recanalization of CTO-RCA may impact on the long-term cardiac-mortality in patients with ULM-PCI.

Disclosures

None.

References


Impact of Residual Chronic Total Occlusion of Right Coronary Artery on the Long-term Outcome in Patients Treated for Unprotected Left Main Disease: The Milan and New-Tokyo Registry

Kensuke Takagi, Alfonso Ielasi, Alaide Chieffo, Sandeep Basavarajaiah, Azeem Latib, Matteo Montorfano, Mauro Carlino, Hiroyuki Mizuno, Tasuku Hasegawa, Cosmo Godino, Filippo Figini, Joanne Shannon, Ahmed Rezq, Santo Ferrarello, Chiara Bernelli, Toru Naganuma, Yusuke Fujino, Sunao Nakamura and Antonio Colombo

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WHAT IS KNOWN

- The presence of chronic total occlusion of right coronary artery (CTO-RCA) may be associated with a worse clinical outcome in patients undergoing unprotected left main (ULM)-PCI due to more severe comorbidities.

- There is little data available regarding the impact of successful recanalization for CTO-RCA on long-term mortality in patients with ULM.

WHAT THE STUDY ADDS

- Cardiac-death occurred more frequently in patients with untreated CTO-RCA as compared to those with successfully recanalized CTO-RCA despite similar comorbidities, while in-stent restenosis (ISR) occurred less frequently in patients with untreated CTO-RCA.

- An occluded RCA has negative impact on the long-term cardiac-mortality in patients undergoing ULM-PCI.
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