Randomized Controlled Comparison of Optimal Medical Therapy with Percutaneous Recanalization of Chronic Total Occlusion (COMET-CTO)

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Summary

The aim of this randomized prospective study was to evaluate the quality of life (QoL) using the “Seattle Angina Questionnaire” (SAQ) in patients with chronic total occlusion (CTO) in coronary arteries treated with either percutaneous coronary intervention (PCI) or optimal medical therapy (OMT), or only with OMT. The potential benefits of recanalization of CTO by PCI have been controversial because of the scarcity of randomized controlled trials.

A total of 100 patients with CTO were randomized (1:1) prospectively into the PCI CTO or the OMT group (50 patients in each group). There were no baseline differences in the SAQ scores between the groups, except for physical limitation scores (P = 0.03). During the mean follow-up (FUP) of 275 ± 88 days, patients in the PCI group reported less physical activity limitations (72.7 ± 21.3 versus 60.5 ± 27, P = 0.014), less frequent angina episodes (89.8 ± 17.6 versus 76.8 ± 27.1, P = 0.006), better QoL (79.9 ± 22.7 versus 62.5 ± 25.5, P = 0.001), greater treatment satisfaction (91.2 ± 13.6 versus 81.4 ± 18.4, P = 0.003), and borderline differences in angina stability (61.2 ± 26.5 versus 51.0 ± 23.7, P = 0.046) compared to patients in the OMT group. There were no significant differences in SAQ scores in the OMT group at baseline and during the FUP. There was a statistically significant increase in all five domains in the PCI group.

Symptoms and QoL measured by the SAQ were significantly improved after CTO PCI compared to OMT alone.

Key words: Arterial occlusive diseases, Percutaneous coronary intervention, Outcome, Quality of life, Seattle Angina Questionnaire

Recanalization of chronic total occlusion (CTO) by percutaneous coronary intervention (PCI) is considered to be one of the most complex coronary interventions. The prevalence of CTO was observed in 16-18% of patients undergoing angiography. However, only 5% were referred for CTO recanalization procedures. Successful CTO recanalization was observed to lead to better clinical outcomes and improved quality of life (QoL). Several randomized studies evaluate the long-term outcomes of treating patients with CTO, but their results are truly controversial, including major adverse cardiac events (MACEs) and QoL. Patients with CTO usually present with atypical symptoms and have well-developed collateral circulation. On the contrary, studies have shown that CTOs can induce ischemia despite well-developed collateral circulation.

Multiple meta-analyses have compared successful with failed PCI of CTO, and significant reductions in short- and long-term mortalities have been shown. To date, there is still a need for large randomized trials to test the effects of PCI of CTO on both clinical outcomes and the patient’s QoL and overall well-being.

The primary endpoint of the study was to compare the QoL and overall well-being in patients randomized to PCI of CTO or optimal medical therapy (OMT) alone using the SAQ. A secondary endpoint of the study was the assessment of all causes of death, acute myocardial infarction (MI), and recurrent revascularization during the...
follow-up (FUP). We also evaluated the change in left ventricular ejection fraction (LVEF) between the baseline and after the FUP period.

**Methods**

**Study design and population:** The sample size of the trial was calculated based on the expected difference between groups of ≥10 points in at least one SAQ domain and the expected standard deviation (SD) of 15 points on the SAQ scale, statistical power (1-β) = 0.8, and statistical significance (α) = 0.05. The sample size calculated was 36 patients per group. With an expected cross-over of 5% and those lost during the FUP up to 20%, the final sample size estimated was 50 patients per group.

Between October 2015 and May 2017, 100 patients with CTO of one coronary artery were randomized prospectively according to a computer-generated code (1:1 ratio). On completing the SAQ, patients were randomized into two groups: the first group of patients who would undergo PCI CTO with OMT and the second group of patients with CTO who would receive only OMT (the control group). All PCIs were performed in the catheterization laboratory at the Cardiology Clinic in Belgrade, Clinical Centre of Serbia. The study was registered on ClinicalTrials.gov with the study number NCT02964975.

Patients were considered for randomization if they met the following inclusion criteria: age > 18 years; clinical indication for elective PCI of CTO (stable angina pectoris and/or objective proof of myocardial ischemia and/or proof of myocardial viability in akinetic regions in the territory of CTO); CTO identified on native coronary artery with a reference vessel size equal to or larger than 2.5 mm by visual estimation. In the presence of normal wall motion or hypokinesia of the territory supplied by the CTO artery, no further viability testing was performed. In patients with akinesis or dyskinesia in the CTO territory, viability assessments were performed by myocardial scintigraphy.

The exclusion criteria were an angiographically significant stenosis in the non-CTO coronary artery, MI in the previous 90 days, contraindications for dual antiplatelet therapy, unsigned informed consent, CTO of the bypass graft, LVEF ≤ 25%, cerebrovascular insult or transient ischemic attack in the last 6 months, severe renal failure, other severe clinical conditions with a life expectancy of less than 1 year, and unwillingness to participate in the FUP period. In the presence of progressive angina that could not be controlled by OMT, the protocol allowed these patients to cross to the revascularization group. The study was approved by the Medical Ethical Committee of the Clinical Center of Serbia, and all patients provided informed consent to participate in the study. All methods were carried out in accordance with the relevant guidelines and regulations.

**Definitions and endpoints:** Coronary CTO was defined as angiographic evidence of total occlusion with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 within a major epicardial coronary artery at least 2.5 mm in diameter and an estimated duration of at least 3 months.\(^{13}\)

The primary endpoint was to evaluate and compare the changes in the patient’s QoL and overall well-being assessed by the SAQ in patients randomized to PCI of CTO with OMT or to OMT alone. OMT consisted of antiplatelet therapy, anti-ischemic therapy, and aggressive...
lipid and blood pressure control.

The secondary endpoints of the study were all-cause mortality and MACE, defined as nonfatal MI and recurrent coronary revascularization (PCI or coronary artery bypass grafting (CABG)). MI was defined as symptoms of cardiac ischemia and a troponin level with at least one value above the ninety-ninth percentile upper reference limit according to the recent guidelines.15) Coro-

Angiographic success was defined as the final residual stenosis < 30% (by visual estimation) and TIMI flow grade 3 after CTO recanalization.13) According to the Academic Research Consortium, stent thrombosis was defined and divided into definitive, probably, and possible.15) Coronary perforations were defined according to the earlier publication of Elis et al.16) Contrast-induced nephropathy was defined as any 24-hour post-procedural increase in creatinine ≥ 25% compared to the basal level.17) The LVEF was obtained by echocardiography using the modified Simpson’s biplane method.18)

### QoL assessment and clinical FUP

QoL was assessed at baseline and at 6 months, by filling out the SAQ. Survival data and cardiac events were obtained at clinical visits during the mean FUP of 275 ± 88 days. The SAQ is a descriptive, self-administered questionnaire that focuses on

### Table I. Baseline Patient and Lesion Characteristics

| Variable                          | OMT n = 50 | PCI n = 50 | P     | Total n = 100 |
|-----------------------------------|------------|------------|-------|---------------|
| Age (years)                       | 63 ± 5     | 61 ± 7     | 0.107 | 62 ± 6        |
| Follow-up (days)                  | 267 ± 93   | 284 ± 84   | 0.354 | 275 ± 88      |
| BMI                               | 27.41 ± 3.46 | 28.40 ± 3.86 | 0.176 | 27.91 ± 3.68  |
| Baseline creatinine (mmol/L)      | 84.44 ± 17.46 | 81.64 ± 15.27 | 0.395 | 83.04 ± 16.38 |
| LVEF                              | 51.34 ± 11.28 | 54.90 ± 9.420 | 0.090 | 53.12 ± 10.49 |
| Male                              | 44 (88)    | 38 (76)    | 0.118 | 82 (82)       |
| Family history of CAD             | 23 (46)    | 24 (48)    | 0.841 | 47 (4)        |
| Hypertension                      | 43 (86)    | 43 (86)    | 1.0   | 86 (86)       |
| Hypercholesterolemia              | 35 (70)    | 36 (72)    | 0.826 | 71 (71)       |
| NIDDM                             | 12 (24)    | 10 (20)    | 0.664 | 22 (22)       |
| IDDM                              | 6 (12)     | 4 (8)      | 0.370 | 10 (10)       |
| Non-smoker                        | 13 (26)    | 20 (40)    | 0.149 | 30 (30)       |
| Ex-smoker                         | 23 (46)    | 14 (28)    | 0.147 | 37 (37)       |
| Current smoker                    | 14 (28)    | 16 (32)    | 0.531 | 33 (33)       |
| PAD                               | 2 (4)      | 2 (4)      | 1.0   | 4 (4)         |
| Previous stroke                   | 4 (8)      | 1 (2)      | 0.169 | 5 (5)         |
| Previous MI                       | 35 (70)    | 29 (58)    | 0.211 | 64 (64)       |
| In-stent CTO                      | 3 (6)      | 5 (10)     | 0.461 | 8 (8)         |
| Angina                            | 0.769      |            |       |               |
| CCS I                             | 11 (22)    | 12 (24)    | 0.23  | 23 (23)       |
| CCS II                            | 26 (52)    | 21 (42)    | 0.47  | 47 (47)       |
| CCS III                           | 11 (22)    | 14 (28)    | 0.25  | 25 (25)       |
| CCS IV                            | 2 (4)      | 3 (6)      | 0.5   | 5 (5)         |
| Reversible ischemia               | 29 (58)    | 26 (52)    | 0.814 | 55 (55)       |
| demonstrated                      | 44 (88)    | 47 (94)    | 0.295 | 91 (91)       |
| Presence of viability             |            |            | 0.060 |               |
| CTO artery                        |            |            |       |               |
| LAD                               | 5 (10)     | 12 (24)    | 0.17  | 17 (17)       |
| Cx                                | 6 (12)     | 10 (20)    | 0.16  | 16 (16)       |
| RCA                               | 39 (78)    | 28 (56)    | 0.67  | 67 (67)       |
| Visual reference VD               | 3.03 ± 0.38 | 2.90 ± 0.30 | 0.60  | 2.96 ± 0.34   |
| Visual length of occlusion        | 20.06 ± 6.40 | 20.46 ± 11.47 | 0.830 | 20.26 ± 9.24  |
| Calcification                     |            |            | 0.585 |               |
| Mild                              | 28 (56)    | 33 (66)    | 0.61  | 61 (61)       |
| Moderate                          | 16 (32)    | 12 (24)    | 0.28  | 28 (28)       |
| Severe                            | 6 (12)     | 5 (10)     | 0.11  | 11 (11)       |
| Proximal cap tapered              | 26 (52)    | 32 (64)    | 0.224 | 58 (58)       |
| Moderate/severe tortuosity        | 2 (4)      | 4 (8)      | 0.513 | 6 (12)        |
| “Interventional” collateral present | 26 (52)  | 22 (44)    | 0.423 | 48 (48)       |
| J-CTO score                       | 1.72 ± 1.09 | 1.48 ± 1.27 | 0.219 | 1.60 ± 1.18   |
| Syntax score I                    | 9.87 ± 3.41 | 10.79 ± 4.89 | 0.822 | 10.33 ± 4.22  |
| EuroSCORE II                      | 0.87 ± 0.34 | 0.80 ± 0.31 | 0.133 | 0.84 ± 0.32   |

Data are expressed as the mean ± SD or as the number (percentage). BMI indicates body mass index; LVEF, left ventricular ejection fraction; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; PAD, peripheral artery disease; MI, myocardial infarction; CTO, chronic total occlusion; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; and VD, vessel diameter. Presence of viability: LV normokinesis or segmental LV hypokinesis or documented viability in CTO territory.
symptoms and impairments in health unique to coronary diseases. The questions are focused on identifying the patient’s perceptions of their symptoms, QoL, and physical function. The five dimensions of coronary artery disease that were measured included physical limitation (PL), angina stability (AS), angina frequency (AF), QoL, and treatment satisfaction (TS). After calculating points from the worst possible level of health or satisfaction achieved, whereas 100 was the best score. Every patient was required to complete the SAQ before randomization and after the FUP period. If the patient could not attend an outpatient visit, a telephonic FUP was conducted (only three patients in the OMT group). There were no statistically significant differences regarding the incidence of the CTO-affected coronary artery between the groups. The procedural characteristics in the PCI group are shown in Table II. The CTO PCI success rate was 47/50 (94%).

**Results**

One hundred patients were randomized to PCI (PCI group; mean age, 61 ± 7 years) and OMT alone (OMT group; mean age, 63 ± 5 years, \( P = 0.107 \)). Figure 1 shows the flowchart of the trial. Patient and lesion characteristics did not differ significantly between the groups at baseline (Table I). The most common coronary artery with CTO in both groups was the right coronary artery (RCA). There were no statistically significant differences regarding the incidence of the CTO-affected coronary artery between the groups. The procedural characteristics in the PCI group are shown in Table II. The CTO PCI success rate was 47/50 (94%).

**Primary endpoint:** A total of 49 patients were analyzed for the primary endpoint in the PCI group and 50 patients in the OMT group. The scores for the five angina-symptom domains at the FUP and their changes from the pre-procedural scores are reported in Table III and Figure 2. Baseline scores were not different between the two groups, except for PL (PCI group 50.7 ± 23.6 versus OMT group 61.3 ± 24.2, \( P = 0.03 \)). During the FUP, patients in the PCI group reported lower physical activity limitations, less frequent angina episodes, better QoL, greater TS, and marginal differences in AS compared with patients in the OMT group (Figure 2). After multivariate regression analysis of changes in the values of all five SAQ domains and different clinical and angiographic variables, only assignment to the study group (Pilli’s trace = 0.342, \( P < 0.001 \)) was associated independently with changes in all five SAQ domains. In the OMT group, scores did not differ significantly for the five SAQ domains at baseline and during the FUP (Figure 2). There

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**Table II. Procedural Characteristics in the PCI Group**

| Variable                                | n = 50 |
|-----------------------------------------|--------|
| Radial approach                         | 9 (18) |
| Contralateral injection                 | 19 (38) |
| First guiding catheter 6Fr              | 21 (42) |
| First guiding catheter 7Fr              | 29 (58) |
| Microcatheter                           | 41 (82) |
| Successful recanalization               | 47 (94) |
| Anterograde recanalization              | 44 (88) |
| Anterograde recanalization: single wire| 28 (64) |
| Anterograde recanalization: step up step down | 16 (36) |
| Retrograde recanalization               | 3 (6)  |
| Total number of wires                   | 2.22 ± 1.61 |
| Total number of balloons                | 2.00 ± 0.97 |
| Number of DES used                     | 1.78 ± 1.02 |
| Maximal diameter of DES (mm)           | 2.98 ± 0.35 |
| Total length of DES (mm)               | 46.84 ± 26.80 |
| Maximal balloon diameter for postdilation (mm) | 3.05 ± 0.36 |
| Time of procedure (minutes)            | 76.06 ± 38.76 |
| Fluoroscopy time (minutes)             | 29.43 ± 20.96 |
| Contrast (mL)                          | 289.60 ± 105.60 |
| Patient dose (mGy)                     | 1295.16 ± 813.98 |

Data are expressed as the mean ± SD or as the number (percentage). DES indicates drug-eluting stent.
was a significant improvement in all five SAQ domains in the PCI group: PL (F = 35.263, df = 1, P < 0.001), AS (F = 21.648, df = 1, P < 0.001), AF (F = 23.449, df = 1, P < 0.001), TS (F = 12.499, df = 1, P = 0.001), and QoL (F = 38.755, df = 1, P < 0.001) (Figure 2).

**Secondary endpoints:** A total of 100 patients were analyzed for secondary endpoints. There were three events in total during the FUP: in the OMT group, two patients underwent PCI revascularization because of impaired angina (cross over), despite maximal antianginal therapy; in the PCI group, only one patient underwent CABG revascularization. During the FUP, there were no deaths, MIs, stent thrombosis, or strokes in either group.

There was no statistically significant improvement in EF during the FUP in both groups (OMT group P = 0.98; PCI group P = 0.057). Medical therapy is shown in Table IV. A significant difference was observed between the baseline and FUP in patients with prescribed adenosine diphosphate antagonists. However, nitrates were prescribed more frequently in the OMT group at baseline and during the FUP.

**Discussion**

This study showed that QoL, evaluated by the SAQ, improved significantly in patients who underwent successful PCI of CTO with OMT compared with patients assigned to OMT alone. During the FUP, we observed a very low rate of revascularizations and no deaths, MIs, stent thrombosis, or strokes in both groups of patients. Also, we have shown a high procedural success rate and a safety profile of CTO recanalization.

Generally, successful PCI of CTO has been associated with various cardiovascular advantages, such as improved wall motion of the affected segment, enhanced LVEF, and reduced arrhythmic vulnerability.20) However, only three randomized trials evaluated the outcomes of PCI of CTO. In addition, health status and QoL indices are used widely in cardiovascular studies and can be important markers for decisions or indications for therapy.

The EURO-CTO (a Randomized Multicenter Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Occlusions) trial enrolled 407 patients with CTO (randomiza-
tion 2:1 - OMT with CTO PCI or OMT respectively), and concluded that in the patients who underwent PCI of CTO, AF (P = 0.003) and QoL (P = 0.007) improved significantly in comparison to patients who received OMT alone. On the other hand, in our study, the PCI group reached the prespecified statistical level of significance for primary endpoints in all five subscales of the SAQ. Also, during the FUP period of 12 months in the EURO-CTO trial, the MACE rate was similar between two groups, but the long-term results (safety) after 36 months still need to be reported.7 These findings are in accordance with our results. Contrary to the EURO-CTO and our study, the DECISION-CTO (Optimal Medical Therapy With or Without Stenting For Coronary Chronic Total Occlusion) trial (417 patients randomized to OMT with PCI of CTO and 398 patients who only received OMT) showed no benefit of CTO revascularization in terms of SAQ subscales at 1 year. The design of this study was different; patients were randomized to OMT or PCI, and all significant non-CTO lesions were treated after randomization and baseline assessment (about 70% of patients in the OMT arm), leading to improvements in the SAQ in the OMT group during the FUP.8

The OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures) observational registry of consecutive patients with CTO undergoing PCI clearly demonstrated significant improvements in the health status, as assessed using the SAQ 1 month after successful CTO recanalization.9

Furthermore, the hazard rate for MACE appears to increase with the increasing complexity of anatomy and CTO intervention.10 Findings from the prospective Consistent CTO study demonstrated that QoL 12 months after successful CTO PCI was improved significantly, as assessed using the SAQ (Simon Wals, MD, unpublished data, 2018). Although the data from the previous three studies contribute to the general understanding of the main purposes for CTO recanalization, the main drawback is that these prospective real-world registries are not randomized clinical trials. As such, these studies provide no information on the outcomes of patients with CTO who did not undergo PCI.

The EXPLORE (Evaluating Xience and Left Ventricular Function in PCI on Occlusions After STEMI) trial included 304 patients who had non-culprit CTO at the time of initial diagnosis of ST segment elevation MI.11 After successful recanalization of the culprit lesion, patients were randomized to OMT with CTO PCI or OMT alone. PCI of CTO proved to be convenient and safe; however, no significant clinical benefits and improvements in the LVEF or left ventricular end-diastolic volume were observed. Furthermore, in patients with recanalization of the left anterior descending artery, there was a significant improvement in the LVEF (47.2% versus 40.4%, P = 0.02). On the other hand, the REVASC trial (a randomized trial to assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion) included 205 patients with CTO (patients were randomized to OMT with CTO PCI or OMT alone) and either clinical symptoms or a positive functional test for ischemia. PCI of CTO did not improve segmental wall thickening at 6 months when evaluating all CTO segments (P = 0.57), or when assessing dysfunctional CTO segments (P = 0.51).

Measures of global left ventricular function, LVEF, and left ventricular end-diastolic volume did not differ between the trial arms. In our study, we found that the LVEF did not improve significantly during the FUP in both the CTO PCI and OMT groups. Above all, a decrease in all-cause mortality in registry data and meta-analysis was related to successful CTO PCI, but large randomized trials are warranted.12 The ORBITA trial, as a blinded, multicenter randomized trial of PCI versus a placebo procedure for angina relief, showed that PCI did not increase exercise time by more than the effect of a placebo procedure for angina relief, showed that PCI did not increase exercise time by more than the effect of a placebo procedure for angina relief. In the COMET-CTO study, patients were aware if they had received a successful PCI; keeping this in mind, we cannot rule out the possibility that the placebo effect had some influence on the study results. This particular issue requires further clarification in the field of CTO.13

Limitations: Our trial was a prospective randomized trial conducted in a single center. The study was not powered to detect differences in the MACE rate as well as all-cause mortality. The success rate of PCI CTO was high (94%) and could positively affect the results of the study.

| Table IV. Medication at Baseline and at Follow-up |
|-----------------------------------------------|
|       | OMT n = 50 | PCI n = 50 | P     |
| Aspirin |           |           |       |
| Baseline | 50 (100)  | 50 (100)  | 1     |
| FUP     | 50 (100)  | 50 (100)  | 1     |
| ADP receptor inhibitors |       |           |       |
| Baseline | 28 (56)   | 50 (100)  | < 0.001|
| FUP     | 14 (28)   | 47 (94)   | < 0.001|
| Beta-blocker |       |           |       |
| Baseline | 41 (82)   | 45 (90)   | 0.249 |
| FUP     | 38 (76)   | 42 (84)   | 0.317 |
| ACE-inhibitors |       |           |       |
| Baseline | 39 (78)   | 35 (70)   | 0.362 |
| FUP     | 36 (72)   | 32 (64)   | 0.391 |
| AT1-antagonist |       |           |       |
| Baseline | 5 (10)    | 6 (12)    | 0.749 |
| FUP     | 7 (14)    | 9 (18)    | 0.585 |
| Calcium antagonist |       |           |       |
| Baseline | 15 (30)   | 11 (22)   | 0.362 |
| FUP     | 18 (36)   | 15 (30)   | 0.523 |
| Statin  |           |           |       |
| Baseline | 49 (98)   | 49 (98)   | 1     |
| FUP     | 47 (94)   | 49 (98)   | 0.307 |
| Nitrate |           |           |       |
| Baseline | 29 (58)   | 15 (30)   | 0.005 |
| FUP     | 24 (48)   | 7 (14)    | < 0.001|
| Trimetazidine |       |           |       |
| Baseline | 24 (48)   | 18 (36)   | 0.224 |
| FUP     | 32 (64)   | 15 (30)   | 0.001 |
| Diuretic |           |           |       |
| Baseline | 16 (32)   | 10 (20)   | 0.171 |
| FUP     | 16 (32)   | 14 (28)   | 0.663 |

Data are expressed as the number (percentage). ACE indicates angiotensin-converting enzyme; ADP, adenosine diphosphate; AT-1, angiotensin-1; FUP, follow-up; OMT, optimal medical therapy; and PCI, percutaneous coronary intervention.
In addition, the high rate of RCA CTOs may affect the outcomes of the trial. In addition, the CTOs described in this manuscript appear to be relatively “simple CTOs” (frequent use of 6F guiding catheters, infrequent dual angiography, vast majority of cases performed by antegrade approach, J-CTO score, etc.). Furthermore, with the complexity of CTO and difficulty of PCI of CTO, the risk of the FUP MACE rate is probably increased, with some potential negative influence on possible symptomatic gain.

Conclusions

Our study demonstrated better overall well-being and improvements in angina symptoms in patients treated with PCI of CTO when compared to patients treated with OMT alone. Our findings suggest that PCI of CTO could improve QoL in symptomatic patients.

Disclosure

Conflicts of interest: The authors declare no conflicts of interest.

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