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Original Research

Treatment of chronic total occlusion with percutaneous coronary intervention is associated with improved survival as compared to medical treatment alone: insights from a single-centre registry

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Symptom relief is currently the main indication to perform percutaneous coronary intervention (PCI) of chronic total occlusion (CTO). So far, none of the randomized trials for CTO treatment have demonstrated improved survival after PCI compared to optimal medical treatment (OMT) alone. We investigated whether CTO PCI in addition to OMT could improve survival over OMT alone. Data of 1004 patients with a treated CTO was analysed. Patients with acute coronary syndrome and who underwent coronary artery bypass graft surgery (CABG) were excluded, thus final study population was 378. According to the treatment received, patients were divided into two groups: CTO PCI + OMT (n = 163) and OMT alone (n = 215). The primary endpoint was all-cause mortality during follow-up. The incidence of myocardial infarction (MI), revascularization (both CTO artery and non-CTO artery related) and stroke were also analysed as a secondary outcome. The mean follow-up period was 3.55 $\pm$ 0.93 years. Multiple regression analysis was performed to identify independent predictors of all-cause mortality. Occurrence of MI and repeat revascularization (both CTO vessel related and non-CTO vessel) and stroke did not differ significantly between groups. However, all-cause mortality was more frequent in OMT (19.1%) patients than PCI (10.4%). Patients age $\leq$70 years (odds ratio (OR) 0.47 [0.26; 0.84], p = 0.01) and CTO PCI (OR 0.51 [0.27; 0.94], p = 0.03) were independent predictors of reduced likelihood of all-cause death. The data from our centre registry demonstrates that CTO PCI is associated with reduced all-cause mortality as compared to medical treatment alone in a real-life setting.

Keywords

Chronic total occlusion; Percutaneous coronary intervention; All-cause mortality

1. Introduction

Chronic total occlusions (CTOs) of coronary arteries are defined as the complete obstruction of a coronary artery with an occlusion duration of >3 months [1]. They are found in 18%–52% of patients undergoing coronary angiography [2–4]. Despite its common prevalence and advances in interventional tools and techniques, only a small percentage of CTOs are treated with percutaneous coronary intervention (PCI). Patients with CTO exhibit symptoms when the collateral supply of blood is insufficient to meet the oxygen demand placed on the myocardial territory [5]. As a result symptom relief is one of the main indication to tackle this patient group, as recommended in the current guidelines by European Society of Cardiology [6]. Data from recent randomized controlled trials (RCTs) comparing medical treatment vs CTO PCI have however demonstrated conflicting results regarding improvement in symptoms and quality of life following treatment. These differences might be explained by different trial methodologies [7, 8]. So far, none of the randomized trials for CTO treatment have demonstrated improved survival resulting from interventional treatment as compared to medical treatment alone [7–9]. Published trials of interventional CTO treatment suffer from relatively small sample sizes and resulting limited statistical power to evaluate survival. In a view of the lack of data about the impact of CTO revascularization on survival, we sought to examine a registry of CTO treatment in our institution to investigate whether CTO PCI in addition to optimal medical treatment could improve survival over medical treatment alone.

2. Methods

Data was collected retrospectively from a registry of treated patients in a single centre (Vilnius University Hospital Santaros klinikos). During the period of June 2014–December 2018 data of 1004 patients with a treated CTO in one of the major coronary arteries was analysed. The flow chart of our registry is demonstrated in Fig. 1. All patients with acute coronary syndromes were excluded and 470 patients undergoing coronary angiography due chronic coronary syndrome were further investigated. Patients who underwent CABG (n = 92) were excluded from further analy-

sis. According to the treatment received, patients were divided into two groups: those treated by CTO PCI in addition to optimal medical treatment (n = 163) and those who received optimal medical therapy (OMT) alone (n = 215). The treatment decision (OMT or PCI + OMT) usually was made together by the physician and the patient, since there are no hard evidences, which would favor particular CTO treatment modality. CTO PCI was usually attempted using antegrade wire escalation technique in most cases; if unsuccessful, the strategy was changed to antegrade dissection/re-entry or retrograde aproach (mainly reverse controlled antegrade and retrograde tracking technique). The success rate of CTO PCI was 89% (successful CTO PCI was performed to 143 of 163 patients). All patients in both groups received medical treatment as recommended in 2019 European Society of Cardiology (ESC) Guidelines on Chronic Coronary Syndromes [10]. The primary endpoint investigated was all-cause mortality during follow-up. The incidence of MI, revascularization (both CTO artery and non-CTO artery related) and stroke were also analysed as a secondary outcome. The mean follow-up period was 3.55 ± 0.93 years and was similar in both groups.

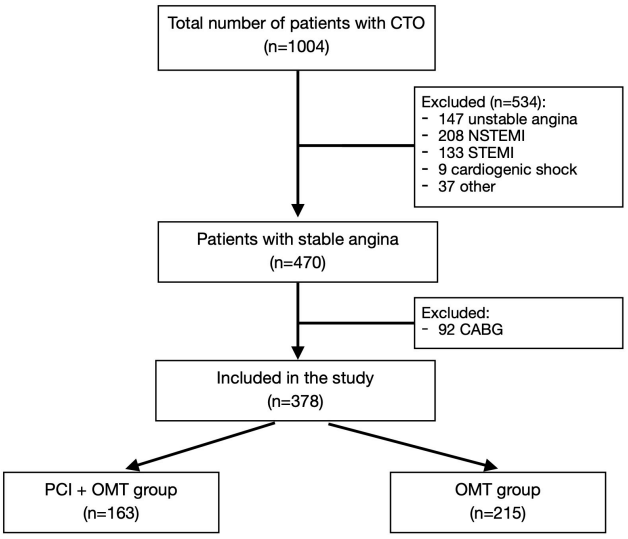

Fig. 1. Clinical trial flow chart.

3. Statistical analysis

Continuous variables were expressed as mean (± standard deviation). Continuous variables with a normal distribution were compared using a Student's *t* test, otherwise, nonparametric Wilcoxon's signed-rank test was used. Categorical variables were expressed as the frequency and compared using the χ^2 test. Univariate regression analysis was performed for the following parameters: age, sex, diabetes mellitus, arterial hypertension, three vessel coronary artery disease (CAD), previous MI and treatment option. To determine the independent associates of all-cause mortality, multiple regression analysis was performed with parameters, which were found to be statistically significant from univariate regression analysis.

4. Results

4.1 Baseline characteristics

Baseline and demographic characteristics are demonstrated in Table 1. The majority of patients were male in both groups. Patients treated with PCI were marginally younger (65.9 years ± 11.3), as compared to patients receiving OMT alone (69.2 years ± 9.4). Diabetes mellitus was more prevalent in PCI group (31.3% vs 22.3%, respectively). Three-vessel CAD was found in one-fourth of patients in both groups. The prevalence of arterial hypertension and previous MI did not differ significantly between two groups.

Table 1. Baseline clinical characteristics of the patients with chronic coronary syndrome according to the received treatment.

Characteristics	PCI, n = 163	OMT, n = 215	*p*
Woman sex, no. (%)	48 (29.4%)	50 (23.3%)	0.174
Age, mean ± SD	65.9 ± 11.3	69.2 ± 9.4	0.003
Age ≤70 years, no. (%)	96 (58.9%)	108 (50.2%)	0.094
Diabetes mellitus, no. (%)	51 (31.3%)	48 (22.3%)	0.050
Arterial hypertension, no. (%)	148 (90.8%)	197 (91.6%)	0.777
Three-vessel CAD, no. (%)	43 (26.4%)	52 (24.2%)	0.626
Previous MI, no. (%)	106 (65.0%)	157 (73.0%)	0.094

PCI, percutaneous coronary intervention; OMT, optimal medical treatment; SD, standard deviation; MI, myocardial infarction; CAD, coronary artery disease.

4.2 Follow-up

Results related to follow-up are presented in Table 2. A mean follow-up period was 3.55 ± 0.93 years and was similar in both groups. Occurrence of MI and repeat revascularization (both CTO vessel related and non-CTO vessel) and stroke did not differ significantly between groups. However, all-cause mortality was more frequent in OMT (19.1%) patients than PCI (10.4%).

Table 2. Cardiovascular outcomes and parameters during follow-up.

Characteristics	PCI, n = 163	OMT, n = 215	*p*
Length of follow up, years ± SD	3.56 ± 0.93	3.55 ± 0.92	0.845
MI, no. (%)	11 (6.7%)	13 (6.0%)	0.782
CTO vessel MI, no. (%)	6 (3.7%)	11 (5.1%)	0.505
CTO vessel revascularization, no. (%)	2 (1.2%)	3 (1.4%)	0.887
Revascularization, no. (%)	15 (9.2%)	15 (7.0%)	0.428
Stroke, no. (%)	1 (0.6%)	2 (0.9%)	0.731
All-cause mortality, no. (%)	17 (10.4%)	41 (19.1%)	0.021

PCI, percutaneous coronary intervention; OMT, optimal medical treatment; SD, standard deviation; MI, myocardial infarction; CTO, chronic total occlusion.

4.3 Prognostic factors of all-cause mortality

Prognostic factors of all-cause mortality are presented in Tables 3,4. Univariate linear regression analysis showed that patients age, presence of three-vessel CAD and treatment option correlated with all-cause mortality. We combined these variables in multivariable logistic regression analysis, which revealed that patients age ≤70 years (OR 0.47 [0.26; 0.84], $p = 0.01$) and CTO PCI (0.51 [0.27; 0.94], $p = 0.03$) were associated with reduced likelihood of all-cause death.

Table 3. Odds ratios for all-cause mortality in univariate logistic regression analysis.

Predictor	p	OR (95% CI)
Woman sex	0.523	1.223 (0.659; 2.272)
Age	<0.001	1.078 (1.042; 1.114)
Age ≤70 years	0.004	0.425 (0.238; 0.758)
Diabetes mellitus	0.363	1.328 (0.721; 2.445)
Arterial hypertension	0.331	0.644 (0.266; 1.563)
Three-vessel CAD	0.037	1.887 (1.040; 3.422)
Previous MI	0.413	1.303 (0.692; 2.455)
Treatment option (PCI)	0.023	0.494 (0.269; 0.906)

CAD, coronary artery disease; PCI, percutaneous coronary intervention; OR, odds ratio; CI, confidence interval.

Table 4. Odds ratios for all-cause mortality in multivariate logistic regression analysis.

Predictor	p	OR (95% CI)
Age ≤70 years	0.011	0.466 (0.259; 0.838)
Three-vessel CAD	0.057	1.806 (0.982; 3.324)
Treatment option (PCI)	0.032	0.508 (0.274; 0.943)

CAD, coronary artery disease; PCI, percutaneous coronary intervention; OR, odds ratio; CI, confidence interval.

5. Discussion

The present registry was designed in a large interventional cardiology centre with significant PCI and CABG volume. The success rate of CTO PCI was 89%, which is considered high in the contemporary setting. The main finding of our study is that CTO PCI alongside optimal medical treatment is associated with a lower all-cause mortality compared to medical treatment alone. Although OMT patients were marginally older than PCI group patients, multivariate regression analysis has demonstrated that treatment option is an independent predictor of all-cause mortality.

Our registry's main discovery that CTO PCI is associated with improved survival contrasts to previously performed RCT trials. All the trials we have assessed have some factors, which prevent long term data on survival after CTO PCI being fully evaluated, i.e., the EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) trial analysed whether patients with ST-Elevation Myocardial Infarction (STEMI) and concurrent CTO in a non-infarct-related artery benefit from additional PCI of CTO shortly after primary PCI [11]. 304 patients were enrolled in this study and the success rate of CTO PCI was 73%. CTO PCI did not result in lower mortality rates compared to medical treatment. However, the EXPLORE trial had a relatively short follow-up of 4 months and we suggest that a longer follow-up is needed in order to investigate any benefit CTO PCI to survival. Similarly, the EuroCTO (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) trial, which enrolled 396 patients, randomly assigned in 2:1 fashion to CTO PCI and OMT alone, did not find a significant difference between groups in respect of all-cause mortality during the 12 month follow up [8]. The largest RCT trial comparing CTO PCI with medical treatment – the DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion) trial has enrolled 834 patients. The median follow-up was 4 years, however, during this relatively long follow-up CTO PCI did not improve survival, as compared to OMT alone [7]. This study however was stopped early due to difficulties with patient enrolment. In addition, the cross-over rate was high (19.6% patients crossed over to receive CTO PCI within 3 days of randomization), and the study was underpowered to detect difference in mortality as an end-point. The IMPACTOR-CTO (Impact on Inducible Myocardial Ischemia of Percutaneous Coronary Intervention versus Optimal Medical Therapy in Patients with Right Coronary Artery Chronic Total Occlusion) trial randomized 94 patients with isolated right coronary artery CTO to PCI or OMT alone [9]. Survival did not differ among the two groups during 12 months follow-up, however, this finding could also be attributed to relatively small patient number and short follow up.

Despite novel tools and techniques used to perform CTO PCI, increasing operator experience and growing procedural success rate, to date, none of the RCTs focusing on CTO have ever demonstrated that CTO revasularization improves survival as compared to medical treatment. The reasons for this may be multifactorial and include difficulties in achieving significant patient numbers, relatively high cross-over rates and short follow-up. Selection criteria and dependent on the chances of a successful PCI may also play a part. Although the outcomes from RCTs have shown no benefit to survival for CTO PCI a few observational studies and a meta-analysis have demonstrated that there could be benefit. Khan *et al.* [12] performed a meta-analysis of 23 observational studies comparing patients with successful CTO recanalization and those managed conservatively. They found that successful recanalization of a CTO results in improved all-cause mortality (relative risk [RR] of 0.54, 95% confidence interval [CI] (0.45–0.65), p-value < 0.001). Interesting observational study with similar follow up duration to our trial (3.5 years) was conducted by Flores-Umanzor *et al.* [13], who reported that CTO PCI reduced all-cause and cardiac mortality among older (≥75 years) patients compared to medical treat-

ment alone. Gerber *et al.* [14] performed an observational trial and found that CTO PCI is associated with improved 3-years survival compared to medical treatment, when it is demonstrated that the myocardium supplied by the treated vessel is viable. These results are in line with our findings, however, myocardial viability was not routinely assessed in our centre.

We conclude that there is a beneficial role for registry data in providing gaps in the knowledge of the clinical relevance of CTO PCI and providing evidence that this form of treatment is effective and can result in longer survival.

6. Study limitations

The results of our study, however, should be interpreted in a view of certain limitations. First of all, due to limited data in multivariate regression analysis, we cannot ascertain, that all important factors that could contribute to all-cause mortality were identified. We recognise the possibility of selection bias in our study, i.e., the PCI group had a slightly younger average age and possibly their coronary anatomy was more favourable to intervention. Also, we do not have data regarding heart failure status (New York Heart Association (NYHA) class), ejection fraction and myocardial viability. We look forward to the results of larger RCTs such as the ongoing NOBLE-CTO (The NOrdic-Baltic Randomized Registry Study for Evaluation of PCI in Chronic Total Coronary Occlusion) and ISCHEMIA-CTO (Revascularisation or Optimal Medical Therapy of CTO) trials, which should provide some useful insights, however, they are estimated to be completed in 2037 and 2028, respectively.

7. Conclusions

The data from our centre registry demonstrates that percutaneous coronary intervention of a chronic total occlusion is associated with reduced all-cause mortality as compared to medical treatment alone in a real-life setting.

Author contributions

AB designed the research study. PB wrote original daft. VB, IMS and AB performed the research. VB, IMS and PB analyzed the data. MR, GD, AB and PB reviewed and edited original draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the clinical trials committee of our institution approved the protocol (CTO-01/1.1). All patients provided informed consent for treatment according to good clinical practice.

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Conflict of interest

The authors declare no conflict of interest.

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