

Successful recanalisation of isolated chronic total occlusions improves outcomes in long-term observation: a case-control study

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Abstract

Background and aim: The long-term benefit of percutaneous recanalisation of chronic total occlusion (CTO) is still unclear. Given advances in interventional cardiology over the last two decades, we sought to investigate whether a successful percutaneous coronary intervention for CTO (PCI-CTO) improves outcomes in an age- and gender-matched single-centre cohort of stable angina patients.

Methods: Out of 401 consecutive patients enrolled to the CTO-Registry database, 276 patients were included in the final analysis. Patients with unsuccessful PCI-CTO (n = 138) were age- and gender-matched in a 1:1 ratio with patients who underwent a successful procedure. The primary end-points included hard end-points comprising death and nonfatal myocardial infarction (MI) and a composite safety outcome measure of death, nonfatal MI and ischaemia-driven revascularisation. The secondary end-point was improvement in angina status or complete resolution of angina symptoms. Patients were followed up for six months and at two years.

Results: Patients who underwent a successful recanalisation of CTO, compared to those who underwent an unsuccessful procedure, revealed similar rates of composite death and MI at six months (0.7% vs. 1.4%; hazard ratio [HR], 0.50; 95% confidence interval ratio [CI], 0.05–4.80; p = 0.56) and two years (1.4% vs. 5.8%; HR 0.24; 95% CI 0.07–0.85; p = 0.053). A significant difference in composite safety end-points between subsets, although not recorded after six months of observation (8.7% vs. 15.2%; HR 0.54; 95% CI 0.27–1.07; p = 0.095), was noted at two years follow-up (15.2% vs. 29.7%; HR 0.47; 95% CI 0.29–0.77; p = 0.004). A greater improvement in symptom burden or resolution of angina symptoms was documented after a successful PCI at both six months (68.1% vs. 23.2%, p < 0.001; 80.4% vs. 34.8%, p < 0.001, respectively) and two years (52.2% and 8.0%, p < 0.001; 68.1% vs. 22.5%, p < 0.001, respectively).

Conclusions: Successful recanalisation of CTO improves outcomes in long-term observation.

Key words: chronic total occlusion, percutaneous coronary intervention, single-vessel disease

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INTRODUCTION

There is little data regarding the outcomes after percutaneous coronary intervention (PCI) for chronic total occlusions (CTO)

[1–6]. The treatment of CTO remains a challenge and is associated with more frequent peri-procedural complications [2, 3]. Therefore it is critical for clinicians to balance the risks

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and benefits of PCI-CTOs when making therapeutic decisions [7]. Recently published studies assessing the benefits of treating CTOs with PCI have included patients with multi-vessel disease as well as isolated CTO; this limited the ability to determine the benefits from PCI-CTO [1, 4]. The patients included in the multicentre studies and registries were mostly heterogeneous which resulted in diversified populations and a potential selection bias [3, 6]. Confounding baseline discrepancies remain a major concern in cohort studies [8]. The matched design potentially increases the precision in a cohort observational study and effectively reduces potential bias [8].

Herein we present a study to assess whether a successful PCI for isolated CTO improves long-term outcomes comprising the hard end-points, composite safety outcome measure of death, nonfatal myocardial infarction (MI), ischaemia-driven revascularisation and angina improvement. The analysis was performed in an age- and gender-matched setting.

METHODS

Study population and data extraction

The CTO Registry contained patients with CTOs of native coronary arteries, symptomatic angina and estimated time of coronary occlusion of at least 30 days. A majority of the patients were excluded due to accelerating angina symptoms or the presence of non-CTO lesions requiring concomitant revascularisation within 30 days. All non-CTO lesions were treated in different settings and were patent at the time of PCI-CTO. Out of 401 consecutive patients enrolled between 2005 and 2007 to the CTO-Single-Centre-Registry database, 276 patients were included in the present case-control analysis. Case subjects ($n = 138$) were consecutive patients who met the inclusion criteria and in whom recanalisation of CTO failed (Table 1). Each case was paired with a control subject. Controls ($n = 138$) were patients with an isolated CTO who underwent a successful recanalisation of an occluded coronary artery. The case and control subjects were matched by two key potential confounders: age using the one year age bands and gender (1:1 pair-wise matching). Matching was performed by

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Chronic total occlusion of native coronary artery
Symptomatic angina
Viable myocardium in stress echocardiography in the territory of the occluded artery
Time of occlusion estimated to be at least 30 days
True CTO (TIMI 0) or functional CTO (TIMI 1) based on baseline angiography
Exclusion criteria
Acute cardiac syndromes or change in exercise tolerance within last 30 days
Non-CTO stenoses requiring concomitant intervention
CTO of vein-grafts and reocclusions of native coronary arteries

CTO — chronic total occlusion; TIMI — thrombolysis in myocardial infarction

an investigator blinded to the outcomes. The flow of patients recruited for the analysis is shown in Figure 1.

This study was previously approved by the local Medical Ethics Committee of the Medical University of Gdansk, Poland.

Angiography and procedural features

Coronary angiography was performed in all patients via the femoral route with the use of validated methods. Intravenous heparin was given at the start of the procedure to maintain an activated clotting time of greater than 200 s. The choice of guiding catheters, guidewires and the use of drug-eluting or bare-metal stents was left to the discretion of the physician. Stents were implanted in all patients with procedural success. Procedural success was defined as residual stenosis of $< 10\%$ with TIMI flow grade 3 in the absence of residual dissection, in-hospital death, acute MI or the need for urgent coronary artery bypass grafting (CABG). All operators were trained in the same academic institution, and therefore the procedure technique was based on a single-centre experience.

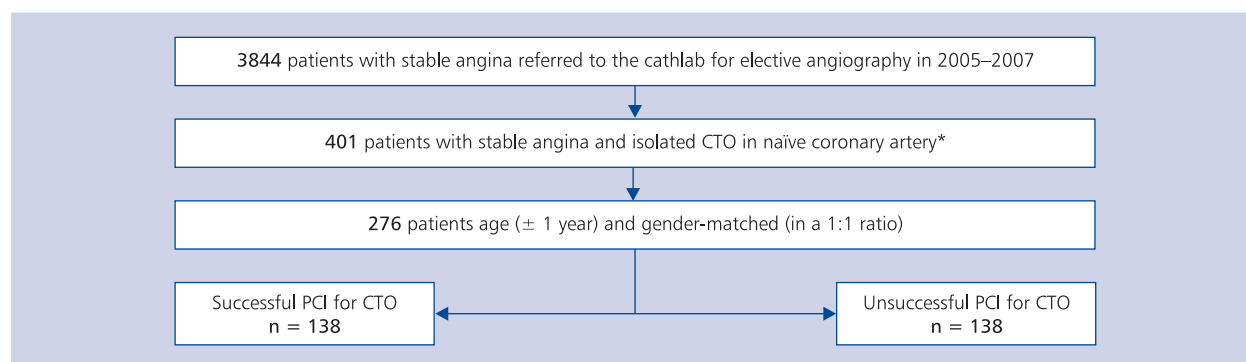


Figure 1. Study design; *isolated CTO — significant ($\geq 50\%$) non-CTO lesion requiring revascularisation within 30 days from the index procedure; CTO — chronic total occlusion; PCI — percutaneous coronary intervention

Study end-points

Clinical follow-up examinations were performed at six months and two years. The events were classified by investigators prospectively during clinical visits or telephone interviews with the use of a dedicated questionnaire.

The primary end-points included hard end-points comprising death and non-fatal MI and a composite safety end-point of major adverse cardiovascular events (MACE) consisting of death, nonfatal MI, symptom-driven subsequent percutaneous and surgical revascularisation (CABG). Symptom-driven target lesion revascularisation (TLR) was defined as the necessity for another intervention to treat a luminal stenosis in the stent or within the 5-mm borders proximal or distal to the stent implanted at the indexed procedure due to angina symptoms and/or MI. Target-vessel revascularisation (TVR) was defined as a repeat of any percutaneous revascularisation of any segment of the target vessel. Repeat-PCI (re-PCI) was specified as a symptom-driven PCI in a non-target vessel. While our database did not allow us to distinguish multiple attempts to treat CTO, all symptom-driven revascularisations which occurred within the first 30 days after the baseline procedure were not indexed as MACE.

The secondary end-point was the improvement/regression of ischaemic symptoms, assessed using the Canadian Cardiovascular Society (CCS) angina classification system. We dichotomised that outcome into an indicator variable defined by improvement of at least two CCS classes and a complete resolution of symptoms at six months and two years.

Statistical analysis

We performed a retrospective analysis of the data prospectively collected in the registry database. Continuous data was presented as mean values (\pm standard deviation) while categorical data was expressed in proportions. Baseline characteristics were compared using the Pearson's χ^2 tests for categorical variables and Student's t-test for continuous variables. Kaplan-Meier product limits were calculated for cumulative probability of reaching a composite safety outcome measure of death, nonfatal MI and ischaemia-driven revascularisation. The hard and secondary end-points were compared using log-rank test for evidence of statistically significant differences between patients treated successfully and those treated unsuccessfully. P-values of less than 0.05 were considered significant in those analyses and all tests were two-sided. We used MedCalc Software (Version 12.3.0, Belgium) for all analysis.

RESULTS

Baseline characteristics

The average age of patients was 61.6 ± 9.7 years and 111 (80.4%) were men in both analysed groups. Baseline characteristics including the prevalence of cardiovascular risk factors and symptom burden were also similar in both groups. In patients with PCI-CTO success compared to PCI-CTO failure there were more

single-vessel disease cases. However, all non-CTO lesions were completely revascularised at the time of attempted PCI recanalisation of CTO. Baseline characteristics are summarised in Table 2.

Clinical outcomes

Patients who underwent a successful recanalisation of CTO, compared to those who underwent an unsuccessful procedure, revealed similar rates of composite death and nonfatal MI in a six-month (0.7% vs. 1.4%; hazard ratio [HR], 0.50; 95% confidence interval ratio [CI], 0.05–4.80; $p = 0.56$) and a two-year follow up (1.4% vs. 5.8%; HR 0.24; 95% CI 0.07–0.85; $p = 0.053$). The significant difference in composite safety end-point between both subsets, although not recorded after six months of follow up (8.7% vs. 15.2%; HR 0.54; 95% CI 0.27–1.07; $p = 0.095$), was noted at the two years follow-up (15.2% vs. 29.7%; HR 0.47; 95% CI 0.29–0.77; $p = 0.004$) (Fig. 2). No significant differences were shown between patients treated successfully vs. those treated unsuccessfully at six months and two years in the rate of subsequent TLR/TVR or re-PCI (Table 3). Successful recanalisation of CTO was associated with a lower rate of subsequent CABG (Table 3). A greater improvement in symptom burden was documented after a successful PCI at both six months and two years of follow-up (68.1% vs. 23.2%, $p < 0.001$; 52.2% and 8.0%, $p < 0.001$, respectively) (Table 4). Also after dichotomisation into an indicator variable defined by a complete angina resolution, we were able to find greater resolution/reduction of symptoms in the group after a successful procedure at both six months and two years of follow-up (80.4% vs. 34.8%, $p < 0.001$; 68.1% vs. 22.5%, $p < 0.001$, respectively) (Table 4). There was no influence of CTO location on outcomes when comparing left main stem/left artery descending (LM/LAD) to left circumflex artery/right coronary artery (LCX/RCA) (Table 5).

DISCUSSION

Our study resulted in several key findings. First, a successful recanalisation of CTO significantly reduced MACE rate at two years of follow-up. Second, we found that angina improvement and its complete resolution were more often documented after a successful PCI-CTO. Third, there was no influence of CTO location on outcomes comparing LM/LAD to LCX/RCA.

The overall rate of CTO recanalisations is still very low. In the United States, only 13.7% of CTOs are recanalised [9]. In the analysis obtained on the basis of the National Heart, Lung, and Blood Institute Dynamic Registry (NHLBI), 5% of all PCIs were carried out for CTO [10]. The guidelines and studies do not address directly whether recanalisation should involve PCI or surgical treatment and in which patients it should be considered a priori [7, 11]. Although the PCI-CTO of the LAD vs. LCX or RCA has been described to be associated with improved long-term survival, we were not able to document that relation in our subset [12].

Table 2. Baseline characteristics of the study population (n = 276)

Variable	Success (n = 138)	Failure (n = 138)	P
Age, mean [years]	61.6 ± 9.7	61.6 ± 9.7	0.96
Male	111 (80.4%)	111 (80.4%)	> 0.99
Cardiovascular risk factors	Success (n = 138)	Failure (n = 138)	P
Myocardial infarction	73 (52.9%)	68 (49.3%)	0.55
Hypertension	85 (61.6%)	78 (56.5%)	0.39
Hypercholesterolaemia	53 (38.4%)	46 (33.3%)	0.38
Diabetes mellitus	31 (22.5%)	26 (18.8%)	0.46
Smoking			
Current	16 (11.6%)	17 (12.3%)	0.85
Former	50 (36.2%)	51 (37.0%)	0.90
CAD	Success	Failure	P
SVD	77/134 (57.5%)	59/135 (43.7%)	0.024
2VD*	35/134 (26.1%)	50/135 (37.0%)	0.054
3VD*	22/134 (16.4%)	26/135 (19.3%)	0.54
Angina symptoms	Success (n = 138)	Failure (n = 138)	P
CCS I	3 (2.2%)	6 (4.3%)	0.31
CCS II	58 (42.0%)	57 (41.3%)	0.90
CCS III	52 (37.7%)	52 (37.7%)	> 0.99
CCS IV	25 (18.1%)	23 (16.7%)	0.75
Coronary artery with CTO	Success (n = 138)	Failure (n = 138)	P
LM	0	1 (0.7%)	0.32
LAD	58 (42.0%)	56 (40.6%)	0.81
LCX	36 (26.1%)	27 (19.6%)	0.20
RCA	44 (31.9%)	54 (39.1%)	0.21

*All non-CTO lesions were completely revascularised at the time of attempted percutaneous coronary intervention recanalisation of CTO; CAD — coronary artery disease; CCS — Canadian Cardiovascular Society functional class; CTO — chronic total occlusion; LAD — left artery descending; LCX — left circumflex artery; LM — left main stem; RCA — right coronary artery; SVD — single-vessel disease; 2VD — two-vessel disease; 3VD — three-vessel disease

What are the benefits of PCI-CTO?

This is a frequently asked, and as yet incompletely answered, question in interventional cardiology. Although the PCI has been well validated to reduce cardiovascular events in patients with acute coronary syndrome [13–19], the COURAGE trial and the BARI 2D trial showed no significant difference in outcomes as concerns the management of stable angina with revascularisation vs. optimal medical treatment [20–23]. Numerous studies comparing PCI and optimal medical treatment in patients with stable angina have presented considerable heterogeneity in baseline characteristics or the strategy of interventional approach (i.e. low percentage of stent implantation) [23]. Our main justification for the study is the lack of specificity of benefits to CTO in other studies since prior reports had included diversified populations which increased potential bias [3, 6]. The recently published Euro Heart Survey of Stable Angina showed a significant gender discrepancy in one-year outcomes [24]. Women were significantly more likely to suffer death or MI compared to males [24]. This could be hypothesised based on different adverse effects of treatment in females and

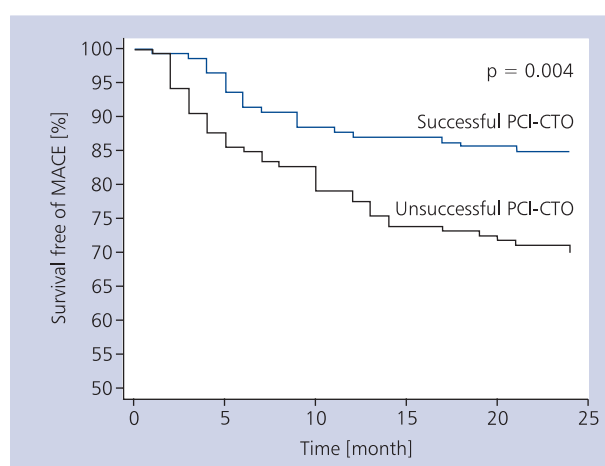


Figure 2. Survival free of major adverse cardiovascular events (MACE); two years of follow up; abbreviations as in Figure 1

males [24]. We should emphasise that the number of patients with a non-CTO lesion requiring PCI concomitant with CTO can

Table 3. Major adverse cardiovascular events in six month and two year observations (n = 276)

Variable	CTO success (n = 138)	CTO failure (n = 138)	HR (95% CI)	P
Six months observation				
Hard end-point*	1 (0.7%)	2 (1.4%)	0.50 (0.05–4.80)	0.56
TLR, TVR	8 (5.8%)	8 (5.8%)	0.98 (0.37–2.62)	> 0.99
Re-PCI	2 (1.4%)	5 (3.6%)	0.39 (0.09–1.73)	0.25
CABG	1 (0.7%)	6 (4.3%)	0.16 (0.04–0.72)	0.056
MACE	12 (8.7%)	21 (15.2%)	0.54 (0.27–1.07)	0.095
Two years observation				
Hard end-point	2 (1.4%)	8 (5.8%)	0.24 (0.07–0.85)	0.053
TVR, TLR	13 (9.4%)	13 (9.4%)	1.75 (1.00–3.07)	> 0.99
Re-PCI	6 (4.3%)	8 (5.8%)	1.23 (0.58–2.63)	0.58
CABG	3 (2.2%)	13 (9.4%)	0.12 (0.04–0.34)	0.010
MACE	21 (15.2%)	41 (29.7%)	0.47 (0.29–0.77)	0.004

*Death + nonfatal myocardial infarction; CABG — coronary artery bypass graft; CI — confidence interval; CTO — chronic total occlusion; HR — hazard ratio; MACE — major adverse coronary events; PCI — percutaneous coronary intervention; re-PCI — PCI of non-target vessel; TLR — target lesion revascularisation; TVR — target vessel revascularisation

Table 4. Angina improvement in six month and two year observations (n = 276)

Variable	CTO success (n = 138)	CTO failure (n = 138)	P
Six month observation			
Angina improvement*	94 (68.1%)	32 (23.2%)	< 0.001
Freedom from angina	111 (80.4%)	48 (34.8%)	< 0.001
Two year observation			
Angina improvement*	72 (52.2%)	11 (8.0%)	< 0.001
Freedom from angina	94 (68.1%)	31 (22.5%)	< 0.001

*Δ CCS ≥ 2 classes

Table 5. Chronic total occlusion localisation and outcomes (n = 276)

Variable	LM/LAD (n = 115)	LCX/RCA (n = 161)	P
Six month observation			
Hard end-point*	1 (0.9%)	2 (1.2%)	0.77
MACE	17 (14.8%)	16 (9.9%)	0.22
Angina improvement**	56 (48.7%)	70 (43.5%)	0.39
Two year observation			
Hard end-point*	5 (4.3%)	5 (4.3%)	0.59
MACE	29 (25.2%)	33 (20.5%)	0.35
Angina improvement**	35 (30.4%)	48 (29.8%)	0.91

*Death + nonfatal myocardial infarction; **Δ CCS ≥ 2 classes; abbreviations as in Tables 1 and 2

be also substantial [1, 6, 25]. Given a perfect balance of data obtained on matched key baseline variables between groups, we could improve efficiency in the estimation of the effect of isolated PCI-CTO on major adverse outcomes [8]. Therefore we performed a study on a highly selected group of patients (1:1 pair-wise matching), where all subjects with successfully treated isolated PCI-CTO underwent stent implantation.

Data on outcomes and symptom improvement/resolution after recanalisation of CTOs are still conflicting [1–6, 26, 27]. No large randomised clinical trials have been performed in this clinically important area [28]. In a large systematic review, successful recanalisation of CTOs was associated with reductions in mortality, CABG and residual or recurrent angina. However, no significant influence on MACE was

documented [29]. In our age- and gender-matched group, successful PCI-CTO compared to unsuccessful PCI-CTO did not reduce significantly the risk of composite death and nonfatal MI, although a strong trend was observed after two years. Furthermore, in contrast to the previously published data, the MACE rate was reduced significantly after a successful procedure at two years of follow-up [5, 29, 30]. A lower CABG rate among patients after a successful PCI-CTO obtained in our highly-selected group has also been reported previously [27, 29]. Moreover, in numerous published studies it is unclear whether TLR/TVR events in the 'unsuccessful group' represent a new attempt at revascularisation of the same lesion. While our database did not allow us to distinguish this possibility based on the clinical data, we excluded any new attempts made within the first month as a TLR/TVR event in the 'unsuccessful group' since this is the practice pattern at our institution.

Limitations of the study

Our study has several limitations. First, this was a single, high-volume centre observation and the experiences at our hospital may not be consistent with those at other facilities where CTOs may be managed differently. In the presented setting of patients with isolated CTOs, only an antegrade approach was performed, which could potentially influence the procedure success.

Second, due to the time period of patient enrollment, we defined the CTO as 100% luminal diameter stenosis, known or assumed to be ≥ 30 days duration based on prior angiography, presence of concordant acute coronary syndrome, severe angina, or a worsening in exercise tolerance. The time duration of CTO in our study did not correspond to the current statement of consensus of the EuroCTO Club where the estimated duration of CTO is three months [31].

Third, the TLR/TVR rates were based on symptom burden and were not evaluated by angiographic follow-up. Therefore TLR/TVR was defined as symptom-driven events.

Fourth, the CCS system to define angina status is not a reliable tool, unlike for example the Seattle Angina Questionnaire, to identify additional factors related to substantial symptom improvement [32, 33]. We were also not able to provide information regarding the ejection fraction among the studied group which could essentially influence long-term outcomes. Moreover, no data on medication use before and after the procedure was included in the analysis. More aggressive medical therapy could potentially attenuate the benefit of successful PCI-CTO over time.

CONCLUSIONS

Our findings support the substantial benefit of successful PCI-CTO for a composite safety outcome measure of death, nonfatal MI and ischaemia-driven revascularisation at two years follow-up. The improvement and complete resolution

of angina symptoms was more often documented after a successful PCI-CTO at either six months or two years of follow-up. Randomised trials are needed to establish a proper treatment strategy for patients with stable angina and CTO.

Conflict of interest: none declared

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Skuteczna rekanalizacja przewlekłych zamknięć naczyń wieńcowych poprawia rokowanie w obserwacji długoterminowej

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Streszczenie

Wstęp i cel: Odległe korzyści z rekanalizacji przewlekłych zamknięć naczyń wieńcowych (CTO) są nadal niepotwierdzone. Uwzględniając postęp w zakresie kardiologii interwencyjnej, który osiągnięto w ciągu ostatnich dwóch dekad, przeanalizowano dane uzyskane z jednego ośrodka i sprawdzano, czy skuteczna rekanalizacja CTO wpływa na rokowanie w grupie osób ze stabilną chorobą wieńcową w porównaniu z dobraną pod względem wieku i płci grupą kontrolną z nieskuteczną rekanalizacją CTO.

Metody: Spośród 401 kolejnych pacjentów włączonych do rejestru CTO (CTO-Registry) 207 zostało zakwalifikowanych do końcowej analizy. Chorzy, u których próba rekanalizacji CTO zakończyła się niepowodzeniem (n = 138), zostali porównani w stosunku 1:1 do dobranej pod względem wieku i płci grupy pacjentów, u których zabieg rewaskularyzacji CTO zakończył się powodzeniem. Ocenianymi pierwszorzędowymi punktami końcowymi były: twardy punkt końcowy obejmujący zgon i zawał niezakończony zgonem i złożony punkt końcowy obejmujący zgon, zawał niezakończony zgonem oraz konieczność ponownej rewaskularyzacji naczynia docelowego (TLR). Drugorzędowym punktem końcowym była poprawa w zakresie klasy czynnościowej dławicy piersiowej lub całkowitej remisji objawów dławicowych. Punkty końcowe oceniano w okresie 6 miesięcy i 2 lat od zabiegu próby rekanalizacji CTO.

Wyniki: Częstość występowania łącznie zgonów z różnych przyczyn i zawałów serca w grupie pacjentów ze skuteczną rekanalizacją CTO w porównaniu z chorymi z nieskuteczną rekanalizacją CTO nie różniła się istotnie statystycznie w obserwacji 6-miesięcznej [odpowiednio: 0,7% vs. 1,4%; iloraz ryzyka (HR) 0,50; 95% poziom ufności (CI) 0,05–4,80; p = 0,56] oraz w obserwacji 2-letniej (1,4% vs. 5,8%; HR 0,24; 95% CI 0,07–0,85; p = 0,053). W obu porównywanych grupach częstość występowania złożonego punktu końcowego nie różniła się istotnie statystycznie w obserwacji 6-miesięcznej (8,7% vs. 15,2%; HR 0,54; 95% CI 0,27–1,07; p = 0,095), natomiast w obserwacji 2-letniej częstość złożonego punktu końcowego była istotnie większa u chorych z nieudaną rekanalizacją CTO (15,2% vs. 29,7%; HR 0,47; 95% CI 0,29–0,77; p = 0,004). Zmniejszenie lub ustąpienie objawów dławicy piersiowej istotnie statystycznie częściej występowało u osób po udanej rekanalizacji CTO w porównaniu z chorymi, u których zabieg rekanalizacji CTO był nieskuteczny, zarówno w obserwacji 6-miesięcznej (odpowiednio: 68,1% vs. 23,2%; p < 0,001; 80,4% vs. 34,8%; p < 0,001), jak i 2-letniej (odpowiednio: 52,2% vs. 8,0%; p < 0,001; 68,1% vs. 22,5%; p < 0,001).

Wnioski: Skuteczna rekanalizacja CTO poprawia rokowanie i redukuje objawy dławicowe u pacjentów w obserwacji długoterminowej.

Słowa kluczowe: przewlekłe zamknięcie naczynia wieńcowego, przezskórna angioplastyka wieńcowa, jednonaczyniowa choroba wieńcowa

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