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Impact of chronic total occlusion artery on 12-month mortality in patients with non-ST-segment elevation myocardial infarction treated by percutaneous coronary intervention (From the PL-ACS Registry)☆

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ABSTRACT

Background: Three-vessel coronary artery disease is associated with high mortality in patients with non-ST-segment elevation myocardial infarction (NSTEMI). The purpose of this study was to assess the impact on 12-month mortality of chronic total occlusion (CTO) in the non-infarct-related artery (non-IRA), as assessed by coronary angiography during percutaneous coronary intervention (PCI) for NSTEMI, of patients with 3-vessel disease.

Methods: The study included all of the NSTEMI patients with 3-vessel disease by coronary angiogram who were treated by PCI and who were registered in the prospective Polish Registry of Acute Coronary Syndromes (PL-ACS) from July 2007 to November 2009. The patients with prior coronary artery bypass grafting and those with significant stenosis of the left main coronary artery were excluded. The 12-month mortality was obtained from a government database.

Results: Of the 925 patients fulfilling the inclusion and exclusion criteria, 438 (47.4%) patients had 1 or more CTO of a major non-IRA coronary artery (+CTO), and 487 (52.6%) patients had 3-vessel disease without CTO (−CTO). The in-hospital mortality for the +CTO and −CTO patients was 5.3% and 2.1%, respectively ($p = 0.009$), whilst the 12-month mortality was 21.1% and 11.9%, respectively ($p = 0.0001$). After multivariate adjustment for differences in the baseline characteristics, the presence of CTO remained significantly associated with higher 12-month mortality (relative risk = 1.42, 95%CI = 1.01–2.00, $p = 0.047$).

Conclusions: The presence of CTO in non-IRA in patients with NSTEMI and 3-vessel coronary disease predicts higher 12-month mortality.

1. Introduction

Non-ST-segment elevation myocardial infarction (NSTEMI) is currently the most frequent manifestation of acute coronary syndromes (ACS) and represents the largest group of patients undergoing percutaneous coronary intervention (PCI) for ACS. Despite advances in medical and interventional treatments, the mortality and morbidity remain high and equivalent to that of patients with ST-elevation myocardial infarction (STEMI) [1]. The presence of chronic total occlusion (CTO) in vessels remote from the infarct-related artery (IRA) in STEMI patients with multivessel coronary disease (MVD) increased early and long-term mortality and was a powerful independent predictor of higher mortality [2,3]. Considering these facts and the limited data available for the NSTEMI population, the objective of this investigation was to evaluate the impact of CTO in non-IRA segments on clinical outcomes whilst in the hospital and during a 12-month follow-up period in patients with NSTEMI and 3-vessel coronary disease who underwent PCI.

2. Materials and methods

2.1. Design of the registry

We used data from the Polish Registry of Acute Coronary Syndromes (PL-ACS). The methodology and analysis of the first 100,193 patients have been previously described [4]. In brief, the PL-ACS registry is one of the largest in Europe. It is an ongoing, nationwide, multicentre, prospective, observational study of consecutively hospitalised patients suffering the entire spectrum of ACS in Poland. The registry is a joint initiative of the Silesian Centre for Heart Diseases and the Polish Ministry of Health. The National Health Fund (NHF), a nationwide public health insurance institution in Poland, provides logistical support. All Polish citizens are required to have a NHF insurance policy.

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The pilot phase of the registry commenced in October 2003 in the Silesia region. In the following months, all of the other regions were activated. Hospitals were invited to enter the registry if they had one of the following wards: coronary care, cardiology, cardiac surgery, internal medicine, or intensive care. They were also invited to join if they hospitalised at least 10 ACS patients per year. A detailed protocol with the inclusion and exclusion criteria, methods and logistics, and definitions of all the fields in the registry dataset was prepared before the registry was started. The protocol was revised in subsequent years to be compatible with the Cardiology Audit and Registration Data Standards (CARDS) [5]. However, the PL-ACS Registry case report form (CRF) covers only part of the CARDS dataset. According to the protocol, all admitted patients with suspected ACS were screened for eligibility to enter the registry, but they were not enrolled until their ACS was confirmed. The patients were then classified as having unstable angina (UA), NSTEMI, or STEMI. If a patient was hospitalised during the same ACS episode in more than one hospital (a transferred patient), all of the hospitals in question were required to complete the registry data. These hospitalisations were linked together during data management and were subsequently analysed as a single ACS case. The data were collected by skilled physicians who were responsible for individual patients. The data were entered directly into an electronic CRF or temporarily printed onto a CRF before being transferred to an electronic CRF. Initial internal checks for missing or conflicting data and values outside of the expected range were implemented within the software. The data were automatically encoded and sent to the NHF once a month, where they were further compared with the patient reports sent by the hospitals. After data verification, the NHF transferred the data to the central database at the Silesian Centre for Heart Diseases in Zabrze, Poland, where further checks were applied. The all-cause mortality data with the accompanying exact dates of deaths were obtained from the official NHF mortality records. The vital status at 12 month post-NSTEMI was available for all of the patients.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Study population and definitions

Between July 2007 and November 2009, a total of 5720 patients with NSTEMI were treated by PCI and registered in the PL-ACS. In this cohort of patients, 1170 (21%) had 3-vessel coronary disease. The patients with prior coronary artery bypass grafting (CABG) (n = 103) and those with significant stenosis of left main (n = 179) were excluded from the analysis. Finally, of the 925 patients fulfilling the inclusion and exclusion criteria and enrolled in this investigation, one or more CTO of the main coronary artery, other than the IRA, was found in 438 (47.4%) patients (+CTO group), and 3-vessel disease without CTO was observed in 487 (52.6%) patients (−CTO group). NSTEMI was defined as the absence of ST-segment elevation consistent with an infarction of ≥2 mm in contiguous chest leads, ST-segment elevation of ≥1 mm in 2 or more standard leads, or a new left bundle branch block and the presence of positive cardiac necrosis markers. Three-vessel coronary disease was defined as ≥70% diameter stenosis in both of the two major epicardial coronary arteries or in their major branches, remote from the IRA, as determined by visual assessment. A coronary artery was considered to be an IRA (culprit) if one of the following criteria was present: definite or suspect thrombus, ruptured or ulcerated plaque, presence of thrombolysis in myocardial infarction (TIMI) flow grade ≤2, and tight stenosis ≥70% consistent with non-invasive ischemia tests. A CTO was defined as a non-IRA with 100% luminal narrowing before PCI and without anterograde flow or with anterograde or retrograde filling through collateral vessels. The differentiation between CTO and acute occlusion was based on a compilation of the following factors: the morphology of the occlusion (the presence of a fresh thrombus image, bridge, and ipsi- or contra-lateral collaterals), the ECG recording, the echocardiogram findings, and a possible history of prior documented acute coronary events in the same territory. The main outcome measures were the in-hospital and 12-month all-cause mortality. The in-hospital outcomes were death from any reason, recurrent MI (defined as an ischemic event that met the European Society of Cardiology/American College of Cardiology criteria for reinfarction and that was evidently clinically distinct from the index event at the time of admission) [6], stroke (defined as an acute neurologic deficit that lasted >24 h and affected the ability to perform daily activities or resulted in death), and major bleedings (defined as overt clinical bleeding that was associated with a drop in haemoglobin of greater than 0.5 g/L or a haematocrit of greater than 15% (absolute), caused haemodynamic compromise or required a blood transfusion.

2.3. Statistical analyses

The continuous variables are presented as means ± SD or as medians and interquartile ranges. The categorical variables are presented as percentages. The continuous variables were compared using the *T*-test or Mann–Whitney *U* test where appropriate, whereas the categorical variables were compared using the Chi-squared test. The twelve-month mortality was analysed using the Kaplan–Meier method. A multivariate Cox proportional hazard model regression was performed to obtain the adjusted influence of CTO in non-IRA on 12-month mortality. Candidate variables entered in the model included age, female sex, diabetes mellitus, hypertension, history of prior MI, history of prior PCI, cardiac arrest before admission, Killip 4 on admission, left ventricular ejection fraction (LVEF), final thrombolysis in myocardial infarction (TIMI) flow grade 3, multivessel PCI and the presence of the CTO. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A two-sided p-value ≤0.05 was considered significant. The STATISTICA 10 software (StatSoft, Inc., Tulsa, OK, USA) was used for all calculations.

3. Results

The baseline clinical and angiographic characteristics of the study groups are presented in Table 1. The patients with CTO were older and had a higher prevalence of previous MI, pulmonary oedema, and cardiogenic shock on admission than the patients without CTO. The in-hospital parameters listed in Table 2 differed significantly between the two groups. The CTO patients had lower LVEF, a higher frequency of initially occluded IRA, and a lower frequency of successful PCI procedures (TIMI flow grade 3 after PCI). However, the extent of the additional revascularisation procedures, both PCI and CABG were similar in the groups. The in-hospital and long-term outcomes analysis is presented in Table 3. A total of 5.3% of the +CTO patients and 2.1% of the −CTO patients (p = 0.009) died during hospitalisation. A significant difference in the mortality rate was also maintained during the 12-month follow-up: 21.2% of the +CTO and 11.9% of the −CTO (p = 0.0001) patients died during that interval (Fig. 1). In the multivariate analysis of the entire study population, the presence of CTO independently increased the risk of 12-month mortality (relative risk = 1.42, 95%CI = 1.01–2.00, p = 0.047) (Fig. 2).

4. Discussion

The current practice guidelines for managing NSTE-ACS published by the European Society of Cardiology (ESC) and the guidelines for myocardial revascularisation created by both the ESC and the European Association for Cardio-thoracic Surgery (EACTS) [7,8] do not recommend a particular modus operandi in subpopulation of patients with NSTEMI and concomitant CTO in non-IRA segments. There are limited data concerning the influence of CTO on the short- and long-term results of PCI for NSTEMI in MVD patients. Knowledge of this relationship might change treatment strategies and improve the outcomes in this high-risk subgroup of patients. The aim of this study was to evaluate the impact of CTO in non-IRA on the prognosis during long-term follow-up in patients with 3-vessel disease who underwent PCI for NSTEMI. The principal finding from this investigation is that the presence of CTO in vessels remote from the IRA in NSTEMI and 3-vessel coronary disease patients increased early and long-term mortality and was also a significant predictor of poor outcome after adjustment in the multivariate analysis. Second, we found that patients with CTO have a higher baseline risk profile and that the presence of CTO did not affected the extent of either percutaneous or surgical coronary revascularisation.

The presence of MVD is noted in about half of the patients with NSTE-ACS and has been associated with poorer clinical outcomes [9–11]. Additionally, three-vessel coronary disease correlates with poorer prognosis in patients with MI [12]. Currently, there is a growing trend towards additional revascularisation, with the complete revascularisation as one of the options, after PCI for myocardial

Table 1
The baseline clinical characteristics of the study groups.

Variable	Chronic total occlusion		p Value
	Yes	No	
	n = 438 (47%)	n = 487 (53%)	
Age, years ± SD	69.8 ± 10	68.4 ± 10.7	0.04
Females, %	35.4	40.5	0.11
Hypertension, %	80.6	77.8	0.30
Diabetes, %	32.9	33.7	0.94
Hyperlipidaemia,%	45.9	41.7	0.19
Current smoking,%	18.5	20.3	0.5
Prior myocardial infarction, %	37.9	20.1	<0.0001
Prior PCI, %	15.8	12.3	0.13
Cardiac arrest before admission, %	0.9	1.2	0.88
Pulmonary oedema on admission, %	4.3	3.5	0.007
Cardiogenic shock on admission, %	4.1	1.6	0.023

PCI, percutaneous coronary intervention.

Table 2
In-hospital data for the study groups.

Variable	Chronic total occlusion		p Value
	Yes	No	
	n = 438 (47%)	n = 487 (53%)	
Mean LVEF, % ± SD	42.5 ± 10.7	47.8 ± 10.6	<0.0001
LVEF ≤ 30%, %	45.3	25.3	<0.0001
Infarct related artery			0.0006
LAD/D	36.3	28.8	
Cx/OM	36.3	32.0	
RCA	27.4	39.2	
IRA baseline TIMI flow grade 0–1, %	40.2	48.3	0.014
IRA final TIMI flow grade 3 after PCI, %	91.6	95.3	0.022
Stent placement (IRA), %	88.1	90.1	0.32
% of DES in IRA (%)	5.7	4.6	0.46
Location of the chronic total occlusion			
LAD/D	30.8		
Cx/OM	33.6		
RCA	58.2		
PCI of 1 additional artery, %	20.3	24.0	0.18
Total revascularisation by PCI, %	5.9	5.3	0.69
CABG during hospitalisation, %	2.1	1.9	0.82
CABG arranged after discharge, %	13.7	14.2	0.84
Hospital stay (days)[a]	5 (4–8)	5 (3–8)	0.3
Pharmacotherapy during hospitalisation			
Aspirin, %	93.6	93.4	0.91
Thienopyridine, %	99.4	98.9	0.76
Glycoprotein IIb/IIIa inhibitor, %	8.9	7.2	0.56
Beta-blocker, %	85.4	88.3	0.19
Angiotensin-converting enzyme inhibitor, %	83.6	86.7	0.19
Statin, %	89.5	91.2	0.39
Nitrate, %	28.8	29.8	0.74
Calcium antagonist, %	12.6	12.1	0.84
Diuretic, %	31.7	26.3	0.068
Aldosterone antagonist, %	6.8	7.6	0.66

CABG, coronary artery bypass grafting; Cx, circumflex artery; D, diagonal branch; DES, drug eluting stent; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; OM, obtuse marginal branch; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.
[a] Median (interquartile range).

infarction. However, there are only limited data concerning the direct, unambiguous mechanisms by which MVD so seriously worsens the long-term outcomes in NSTEMI patients treated by PCI. As one of the factors may be the presence of CTO in non-IRA segments, our study may provide an additional parameter for risk stratification.

The reasons why concurrent CTO affects prognosis so adversely in NSTEMI MVD patients may in part be related to the higher risk profile of CTO patients (older age, more previous MI, lower LVEF, and more cardiogenic shock on admission). After adjustment for these differences in baseline characteristics by multivariate Cox regression analysis, however, CTO remains an independent predictor of 12-month mortality.

Table 3
The in-hospital and long-term outcomes.

Variable	Chronic total occlusion		p Value
	Yes	No	
	n = 438 (47%)	n = 487 (53%)	
In-hospital outcomes			
– TLR during initial hospitalisation, %	1.4	0.6	0.4
– Major bleeding, %	3.7	2.5	0.29
– Stroke, %	0.5	0.0	0.43
– Re-infarction, %	1.1	0.0	0.055
– Death, %	5.3	2.1	0.009
Long-term mortality			
– 30-day, %	8.9	4.3	0.004
– 6-month, %	16.9	10.3	0.003
– 12-month, %	21.2	11.9	0.0001

TLR, target lesion revascularisation.

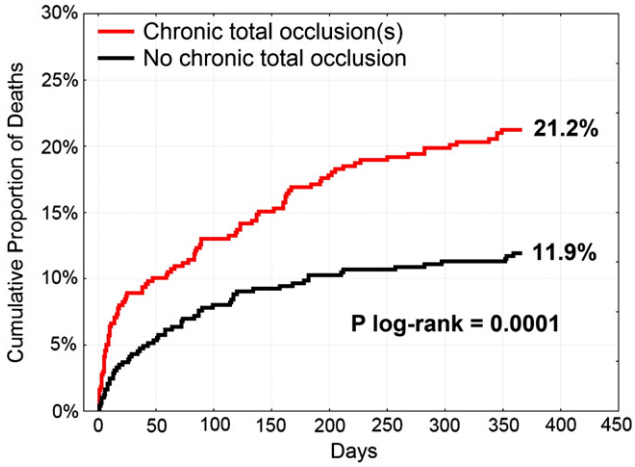

Fig. 1. Twelve-month mortality of the study groups.

Another explanation for the underlying mechanism of the increased mortality in NSTEMI patients with concurrent CTO could be that the PCI was less successful in patients with CTO. A final grade 3 TIMI flow is strongly associated with better prognosis [13], and in our investigation it was more frequently present in the patients without CTO.

An additional factor that may contribute to adverse outcomes in patients with CTO is the lack of a compensation mechanism for the decreased left ventricle function in acute phase MI. The patients with MVD and concomitant CTO have lower residual LVEF and less improvement in LV systolic function, which strongly influence survival after the primary PCI [3]. The patients with NSTEMI and CTO probably had left ventricular dysfunction before their myocardial infarction as a consequence of the greater extent of their coronary artery disease. However it is interesting that more than 60% of the patients in the CTO group had not had a documented MI before admission.

Goldstein et al. have shown that the pathological process in MI involves the entire coronary tree and may lead to the destabilisation and rupture of multiple atherosclerotic plaques, resulting in a significantly increased risk of death and repeated ischemic events [14]. The dynamics of this specific inflammatory process are most significant in the first month following an acute MI [15], possibly explaining the increased mortality rate in the first 30 days observed in our investigation (Fig. 1). It is possible that patients with NSTEMI and MVD, especially the subpopulation of patients with CTO, should be optimally treated, including with surgical revascularisation, as soon as possible. However, this hypothesis requires verification in further investigations.

Previous studies have emphasised that the angiographic extent of coronary artery disease is a simple and easily accessible prognostic measure in patients undergoing PCI for myocardial infarction and should be used to stratify the risk of these patients during acute coronary angiography [16]. Patients with NSTEMI, multivessel coronary artery disease and CTO exhibit many factors adversely influencing their prognosis. In fact, as the patients with CTO have higher early and long-term mortality, new treatment methods should be sought to improve their prognosis. Due to the paucity of data regarding the optimal treatment of patients with NSTEMI and MVD, the need for, method and timing of subsequent revascularisation of diseased non-IRA vessels remains controversial. The current practice guidelines recommend that revascularisation be limited to the culprit lesion, but do not clearly indicate how to optimally proceed after that point [7,8]. A number of the observational studies that compare multivessel PCI during the index event with a culprit-only procedure are hampered by selection bias and have reported inconclusive results [17–19]. Additionally, there is either a lack of data about the

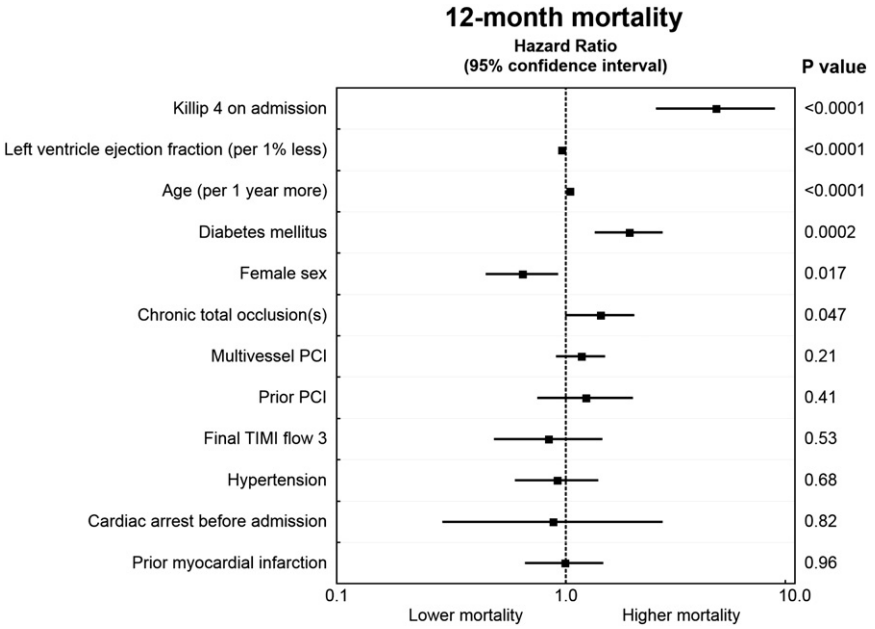

Fig. 2. Predictors of 12-month mortality in the entire study population (Cox proportional hazards model results). Variables are shown in descending order of Wald X^2 values.

presence of CTO or chronic total occlusion is reported as one of the major exclusion factors in these reports. Therefore, the conclusions from these reports do not clearly reflect real-world patients with NSTEMI and MVD. As we currently do not have precise guidelines, recommendations or randomised trials, a complete analysis of each individual total revascularisation case that includes the heart team is warranted, especially in patients with CTO.

4.1. Limitations

There are several limitations of our analysis. The PL-ACS registry is a prospective observational study and not all hospitals treating ACS in Poland participated in data collection. Consequently, the reported significant higher mortality in NSTEMI with CTO patients should be interpreted with caution. Additionally, the retrospective nature of our analysis is a potential weakness. Even after data adjustment, the results could be biased by potentially important parameters that are not available in the registry thus, despite using the multivariable analysis, the conclusions require confirmation by a randomised trial. Finally, as it is a single-country study, it may be not applicable to populations of the other countries.

5. Conclusions

The presence of CTO in non-IRA in patients with NSTEMI and 3-vessel coronary disease predicts higher in-hospital and 12-month mortality.

Contributors

Marek Gierlotka and Mateusz Tajstra — conception and design, acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be published.

Mariusz Gąsior, Michał Hawranek, Tadeusz Osadnik, Krzysztof Wilczek, Krzystof Dyrbuś and Dawid Olszowski — analysis and interpretation of data, revising the manuscript critically for important intellectual content and final approval of the version to be published.

Lech Poloński — conception and design, revising the manuscript critically for important intellectual content and final approval of the version to be published.

Ethical approval

Approval was obtained from local institutional review boards if required.

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