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Impact of the presence of chronically occluded coronary artery on long-term prognosis of patients with acute ST-segment elevation myocardial infarction

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Abstract

Background: *Multivessel disease (MVD) is a significant risk factor in patients with acute ST-segment elevation myocardial infarction (STEMI). Whether the presence of chronic total occlusion (CTO) poses an additional hazard is still unknown. The objective of this study was to evaluate the impact of CTO on survival in STEMI patients.*

Methods: *The study group consisted of 836 STEMI patients treated with primary percutaneous coronary intervention (PCI). MVD was diagnosed in 52.3%, and CTO in 17.5% of patients.*

Results: *In MVD patients, 30-day mortality was 4.8% (6.8% in the CTO and 3.8% in the non-CTO group, p = 0.167). After 6 years, of the 437 patients with MVD, 56 (38.6%) died in the CTO group, and 74 (25.4%) in the non-CTO group (p = 0.0055). CTO was an independent predictor of long-term mortality (OR 2.07, 95% CI 1.30–3.28, p = 0.002), whereas triple vessel disease was not (OR 1.27, 95% CI 0.78–1.97, p = 0.358). The other independent predictors of mortality were: age, anterior myocardial infarction, and PCI failure.*

Conclusions: *The presence of CTO is an independent predictor of the long-term mortality in STEMI patients treated with primary PCI.* (Cardiol J 2017; 24, 2: 117–124)

Key words: acute myocardial infarction, multivessel disease, chronic total occlusion

Introduction

In recent years major developments in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI) have been observed. Rapid restoration of normal blood flow in the infarct-related artery (IRA) with primary angioplasty (percutaneous coronary intervention [PCI]) reduces the infarct size, preserves left ventricular function and improves patients' clinical outcome [1]. In the setting of STEMI, the presence of multivessel disease (MVD) is an important risk factor indicating a worse prognosis [2, 3]. According to current guidelines primary PCI procedure is usually limited to IRA, leaving a substantial number of patients with incomplete revascularization [3]. While MVD is widely recognized as a risk factor, it is not clear whether the presence of a chronic total occlusion (CTO) in a non-IRA poses an additional hazard to patients with STEMI. The aim of this study was to assess the impact of MVD, with particular emphasis on CTO, on short and long-term prognosis of patients with STEMI treated with primary PCI.

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Methods

Study design, objectives and patient selection

This study is a part of prospective registry of consecutive patients diagnosed with acute STEMI, treated with primary PCI at University Hospital in Poznan.

Consecutive patients, admitted between October 2001 and December 2003 were enrolled if they met the following inclusion criteria: typical chest pain persisting for more than 30 min and persistent ST-segment elevation in at least two contiguous leads: > 0.2 mV in leads V2–V3, or > 0.1 mV in other leads, or the presence of a new left bundle branch block. For this analysis patients treated with fibrinolysis prior to PCI were excluded, unconscious patients in cardiogenic shock, those with critical stenosis of the left main coronary artery, as well as patients treated later than 12 h from symptom onset. The study was performed according to the provisions of the Declaration of Helsinki and good clinical practice. Informed consent was obtained from each patient. The study obtained the approval of local Ethics Committee (protocol no 807A/01).

Procedures and follow-up

On admission all aspirin, and clopidogrel-naive patients received a loading dose of both drugs, 300 mg each. The primary PCI procedure was performed via femoral approach in accordance with the standards of the time. After femoral puncture, patients were given a bolus of unfractionated heparin in a dose of 100 U/kg. The use of abciximab was at the discretion of the operator. The flow in coronary arteries was assessed by Thrombolysis In Myocardial Infarction (TIMI) scale. Significant stenosis of coronary artery was diagnosed if diameter stenosis was equal to or greater than 70% by visual estimate. IRA location was diagnosed upon the electrocardiogram (ECG) findings and the typical angiographic image. Single vessel disease (SVD) was diagnosed if significant stenosis was found exclusively in the IRA. MVD was defined as ≥ 70% diameter stenosis in one or more additional major epicardial vessel or their major branches. A CTO was defined as a non-IRA vessel being completely occluded, with no flow or TIMI 1 flow, and a typical angiographic image of chronically occluded artery. In all patients PCI was limited exclusively to the IRA. Standard catheters and bare metal stents were used during procedures. No aspiration thrombectomy devices were used. The PCI procedure was regarded as successful if final TIMI flow in the IRA was ≥ 2, with no major complication during the procedure. On discharge all patients were recommended to remain on dual antiplatelet therapy for 12 months, and then lifelong on aspirin alone.

Study end points

The main outcome measures were 30-day, 12-month, and 6-year all-cause mortality rate among study patients. Additionally in-hospital, 30-day, 12-, and 24-month major adverse cardiovascular events were analysed, including death of any cause, cardiovascular death, stroke, recurrent myocardial infarction (MI) (defined as any spontaneous event with persistent ST-segment elevation and/or new Q-wave formation, or the CK-MB rise 3 times above the limit), and target-vessel revascularization. Patient outcomes at 30 days, 12 and 24 months were assessed by direct visits or telephone contact. The long-term all-cause mortality data were obtained from the Polish National Identification Number Registry (PESEL). None of the patients was lost to the long-term follow-up.

Statistical analysis

All continuous variables are presented as means ± standard deviation or medians, and were compared using a Student t-test. Categorical variables are presented as counts and percentages or frequencies, and were compared using a χ^2 test. Survival curves were plotted using Kaplan-Meier method, and comparisons between groups were done using the log-rank test. The Cox proportional-hazards model was used to identify the independent predictors of mortality. Predictors were selected at $p < 0.1$ in univariate analysis. The significant factors were calculated and expressed as adjusted hazard ratio (HR), with 95% confidence interval (CI). All probability values < 0.05 were considered significant. Statistical analysis was performed using the statistical package STATISTICA 8.1 PL.

Results

Patient population

Between October 2001 and December 2003 a total of 1070 STEMI patients were admitted to the aforementioned department and treated with primary PCI. Of those, 836 met all the inclusion/exclusion criteria and constitute this study group. The baseline demographics and clinical characteristics of the entire population is presented in Table 1. Table 2 summarizes lesion and procedural characteristics of the overall group.

Table 1. Baseline demographics and clinical characteristics of the overall study group (n = 836).

Variable	Patient-based
Age [years]	61.3 ± 11.7
Male	602 (72%)
Previous MI	165 (19.7%)
Hypertension	454 (54.3%)
Diabetes	135 (16.1%)
Current smoker	472 (56.5%)
Peripheral vessel disease	79 (9.4%)
History of PCI/CABG	47 (5.6%)/12 (1.4%)

CABG — coronary artery bypass grafting; MI — myocardial infarction; PCI — percutaneous coronary intervention.

Table 2. Procedural characteristics of the overall study group (n = 836).

Variable	Patient-based
IRA	
LAD	382 (45.7%)
LCX	109 (13.0%)
RCA	345 (41.3%)
MVD	437 (52.3%)
CTO	146 (17.5%)
CTO LAD	40 (4.8%)
CTO LCX	49 (5.8%)
CTO RCA	57 (6.8%)
IRA final TIMI flow ≥ 2	791 (94.6%)

CTO — chronic total occlusion; IRA — infarct-related artery; LAD — left anterior descending; LCX — left circumflex; MVD — multivessel disease; RCA — right coronary artery; TIMI — Thrombolysis In Myocardial Infarction

Table 3. Multivariate Cox proportional hazards analysis of long-term mortality of the overall study group (n = 836).

Variable	OR	95% CI	P
Age	1.06	1.04–1.08	< 0.0001
Chronic total occlusion	2.41	1.59–3.63	< 0.0001
PCI failure	3.42	1.68–6.97	0.0006
Multivessel disease	1.39	0.93–2.09	0.103
Anterior MI	1.41	0.99– 2.01	0.052

CI — confidence interval; MI — myocardial infarction; OR — odds ratio; PCI — percutaneous coronary intervention

On baseline coronary angiography SVD was diagnosed in 399 (47.7%) patients, and MVD in 437 (52.3%), of whom 262 had double-, and 175 triple-vessel disease (31.3% and 20.9%, respectively). The presence of chronically occluded non-IRA was found in 146 patients. Final TIMI flow ≥ 2 was achieved in 791 (94.6%) patients. Thirty-day, and 12-month mortality rate was 31 (3.7%), and 65 (7.8%), respectively. Within the first 12 months recurrent MI occurred in 47 (5.6%) patients, stroke in 15 (1.8%), and target-vessel revascularization in 72 (8.6%). Additionally, 155 (18.5%) patients underwent repeated PCI of non-infarct-related vessel. Surgical revascularization (coronary artery bypass grafting [CABG]) was performed in 17 (2%) patients.The mean and the median time of observation time was 74 ± 27 and 83 months, respectively. During this time 193 (23.1%) patients died — 63 (15.8%) in SVD group, and 130 (29.7%) in MVD group, $p < 0.0001$. The following risk factors correlated significantly with all-cause mortality: age (OR 1.06, 95% CI 1.04–1.0, $p < 0.0001$), history of MI (1.6, 95% CI 1.14–2.43, $p = 0.008$), diabetes mellitus (OR 1.64, 95% CI 1.09–2.47, $p = 0.016$), the presence of MVD (OR 2.25, 95% CI 1.60–3.16, $p < 0.0001$), CTO (OR 2.51, 95% CI 1.71–3.68, $p < 0.0001$), and PCI failure (OR 4.23, 95% CI 2.20–8.14, $p < 0.0001$). Anterior location of MI has shown borderline significance (OR 1.34, 95% CI 0.97–1.85, $p = 0.072$). In multivariate analysis diabetes mellitus, previous MI, and the presence of MVD were no longer significant predictors of death, and only the age, CTO and PCI failure remained significant (Table 3). Kaplan-Meier survival curves of patients with SVD, and MVD with or without the presence of CTO are presented in Figure 1.

Results of multivariate analyses are presented in Table 4. The presence of CTO was not an independent predictor of short-term mortality. Nevertheless, the longer the observation time, the greater the predictive value of CTO. Importantly, a similar relationship could not be found for the presence of MVD, which per se did not correlate with mortality during any observation time.

Analysis of patients with MVD

Of 437 patients with MVD in 146 the presence of CTO was found. Patients in the CTO group, as compared non-CTO group, had a significantly more frequent history of MI and PCI procedure, signifi-

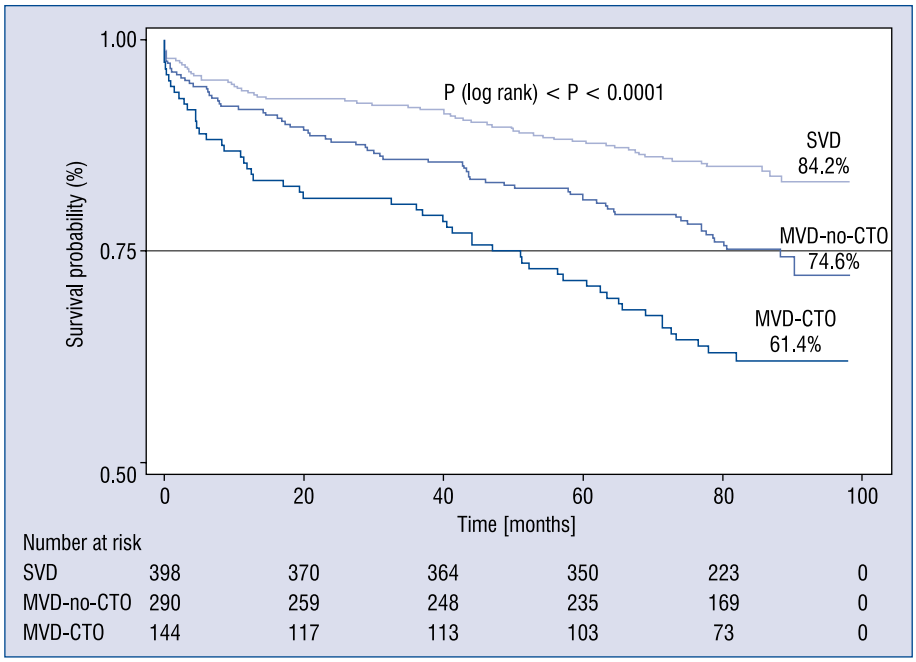

Figure 1. Kaplan-Meier survival curves of patients with single, and multivessel disease (MVD) with and without the presence of chronic total occlusion (CTO); SVD — single vessel disease.

Table 4. Multivariate Cox proportional hazards analysis of all-cause mortality in subsequent periods of observation in the whole group (n = 836).

Observation time		Age	PCI failure	CTO	MVD	Anterior MI
	OR	1.06	2.07	2.18	1.23	1.69
30 days	95% CI	1.02–1.10	0.64–6.71	0.85–5.58	0.50–3.05	0.79–3.60
	p	0.0003	0.222	0.103	0.640	0.171
	OR	1.04	3.75	2.22	1.11	2.23
12 months	95% CI	1.02–1.07	1.64–8.58	1.21–4.08	0.58–2.14	1.28–3.87
	p	0.0001	0.002	0.009	0.737	0.004
	OR	1.05	3.26	2.26	1.1	2.17
24 months	95% CI	1.03–1.08	1.50–7.09	1.34–3.82	0.63–1.92	1.35–3.49
	p	< 0.0001	0.003	0.002	0.715	0.001
	OR	1.06	3.42	2.41	1.39	1.33
6 years	95% CI	1.03–1.06	2.2–3.12	1.35–2.05	0.93–2.09	0.99–2.01
	p	< 0.0001	0.0006	< 0.0001	0.103	0.052

CI — confidence interval; CTO — chronic total occlusion; MI — myocardial infarction; MVD — multivessel disease; OR — odds ratio; PCI — percutaneous coronary intervention

cantly less often anterior location of MI, as well they were more likely to have diabetes, although this difference was not statistically significant. TIMI flow ≥ 2 was achieved in 92.4% of patients with MVD; 93.5% in non-CTO vs. 90.4% in the CTO group (p = 0.177), whereas TIMI 3 flow was achieved in 87.6% of non-CTO patients and in 84.2% of the CTO patients (p = 0.210) (Table 5).

Thirty-day mortality rate of MVD cohort was 4.8% (21 patients). The rate of death in the CTO group was almost double the rate of the non-CTO group (6.8% vs. 3.8%), although this difference

Table 5. Baseline demographics and clinical characteristics of patients with multivessel disease (MVD) (n = 437)

	Total MVD (n = 437)	Non-CTO group (n = 291)	CTO group (n = 146)	P (non-CTO vs. CTO)
Age [years]	63.1 ± 11.7	63.6 ± 11.3	62.5 ± 11.2	0.335
Previous MI	116 (26.5%)	56 (19.2%)	60 (41.1%)	< 0.0001
History of PCI	28 (6.4%)	9 (3.1%)	19 (13.0%)	0.0001
Diabetes	92 (21.1%)	54 (18.6%)	38 (26.0%)	0.074
Current smoker	235 (57.8%)	151 (51.9%)	84 (57.5%)	0.269
Hypertension	252 (57.7%)	168 (57.7%)	84 (57.5%)	0.968
Anterior MI	195 (44.6%)	136 (46.7%)	59 (33.8%)	0.011
Final TIMI flow ≥ 2	404 (92.4%)	272 (93.5%)	132 (90.4%)	0.177

CTO — chronic total occlusion; MI — myocardial infarction; PCI — percutaneous coronary intervention; TIMI — Thrombolysis In Myocardial Infarction

Table 6. Multivariate Cox proportional hazards analysis of all-cause mortality in subsequent periods of observation in patients with multivessel disease (n = 437).

Observation time		Age	PCI failure	CTO	3VD	Anterior MI
30 days	OR	1.07	1.85	1.88	2.39	1.43
	95% CI	1.01–1.11	0.45–7.52	0.70–5.03	0.88–6.47	0.80–3.21
	p	0.005	0.384	0.202	0.085	0.325
12 months	OR	1.03	4.38	1.88	2.16	1.55
	95% CI	1.00–1.06	1.77–10.84	0.96–3.65	1.09–4.26	0.83–2.91
	p	0.041	0.001	0.061	0.026	0.165
24 months	OR	1.05	4.02	2.06	1.32	1.88
	95% CI	1.02–1.08	1.69–9.56	1.15–3.71	0.72–2.40	1.05–3.36
	p	< 0.0001	0.001	0.015	0.355	0.032
6 years	OR	1.06	3.48	2.07	1.24	1.57
	95% CI	1.03–1.08	1.52–7.98	1.30–3.28	0.78–1.97	1.00–2.44
	p	< 0.0001	0.003	0.045	0.358	0.045

CI — confidence interval; CTO — chronic total occlusion; MI — myocardial infarction OR — odds ratio; 3VD — triple vessel disease; PCI — percutaneous coronary intervention

was not statistically significant (p = 0.167). In a multivariate analysis only patient age was an independent predictor of 30-day mortality (OR 1.07, 95% CI 1.01–1.11, p = 0.005).

After 1 year total, cardiac mortality rate was 11% (48 patients), and 10% (44 patients), respectively. Both total and cardiac mortality were significantly higher in the CTO group: for cardiac mortality 22 (15.1%) vs. 22 (7.6%), p = 0.015, for all-cause mortality 23 (15.8%) vs. 25 (8.6%), p = 0.026. After 6 years 129 (29.7%) patients died, of whom 56 (38.6%) in the CTO group, and 74 (25.4%) in the non-CTO group (p = 0.0055).

In univariate analysis we found the following significant risk factors of long-term all-cause mortality: patient's age (OR 1.05, 95% CI 1.02–1.08, p = 0.0001), the presence of triple-vessel disease (OR 1.63, 95% CI 1.07–2.48, p = 0.019), CTO (OR 1.82, 95% CI 1.19–2.82, p = 0.005), and PCI failure (OR 3.69, 95% 1.70–8.00 CI, p = 0.0008). Anterior location of MI has shown borderline significance (OR 1.42, 95% CI 0.94–2.15, p = 0.093). Results of multivariate analysis in subsequent periods of observation are presented in Table 6. The presence of CTO was not an independent predictor of short-term mortality. Nevertheless, the longer the observation time, the greater the predictive value of CTO. It is important to note, a similar relationship could not be found for the presence of triple-vessel disease, which proved to be an independent

predictor of death only at 12 months. In a long-term follow-up, the significant independent predictors of all-cause mortality were patients' age, anterior location of MI, PCI failure and the presence of CTO.

Discussion

Long-term clinical outcomes of a large cohort of STEMI patients treated with primary PCI were reported on. The main objective of the study was to determine the effect and the the extent of coronary artery disease, particularly the presence of CTO, on early and long-term survival.

There were risk factors of early and late mortality such as age, presence of MVD, CTO, anterior location of MI, and PCI failure. The main reason of the failure of PCI was due to slow- or no-flow in IRA. All the procedures were performed in the early years of this century, thus no thrombectomy devices were used at that time. In cases where suboptimal flow was obtained bailout intracoronary abciximab injections were usually performed, sometimes in combination with verapamil, nitroprusside or adenosine. In later years, a new strategy was introduced using upfront high-dose intracoronary adenosine injections with more promising results [4]. MVD is a well-known risk factor in the death of patients with STEMI [2, 3]. Whether the presence of CTO plays an independent role is still a matter of debate. The present study group was not at high risk. In order to eliminate the impact of other powerful risk factors, the following patients were excluded: patients those in a coma, with cardiogenic shock, significant left main stenosis, as well as those of whom reperfusion was achieved after 12 h from symptom onset. This resulted in a low 30-day mortality rate for the entire group (3.7%). This study, like many others, found that MVD was an important risk factor of death in patients with STEMI. However, after taking into account the presence of CTO, the mere presence of MVD was no longer an independent predictor, nor was the presence of triple-vessel disease. Interestingly, the predicting power of CTO grew along with time. In the early period, most likely due to relatively low risk for the whole group, CTO had negligible or borderline impact on survival. Over the years, its relevance grew, being a very strong predictor of death after 6 years. Many recent papers pointed to the importance of CTO in patients with STEMI. van der Schaaf et al. [5], in a 1-year observation of 1417 patients with STEMI reported that the presence of CTO was an independent risk factor of mortality, while the mere presence of MVD was not. What's more, the mortality rate of patients with MVD but without CTO was comparable with the mortality of patients with SVD. The same conclusion could be drawn when looking at the Figure 1 presented in this study. The survival curves of SVD patients, and patients with non-CTO MVD run initially very close to each other, and begin to separate only after 2 years. In a later study of the same group the authors evaluated the effects of CTO on long-term prognosis [6]. They also found that the presence of CTO, but not MVD alone, was associated with long-term mortality, even when early deaths were excluded from the analysis. Polish authors, in a population of 666 STEMI patients with MVD, after 5 years of observation discovered that CTO was an independent predictor of mortality [7]. Importantly, the study group was a high risk one. On admission shock was diagnosed in 22% of CTO patients, whereas in those with non-CTO MVD in 11% ($p = 0.0027$). The CTO group had significantly worse TIMI flow after procedure, and significantly higher in-hospital mortality rate than the rest of the MVD group (21% vs. 6.3%, $p < 0.0001$). After 5 years mortality rate in the CTO group was almost twice as high as in the non-CTO patients with MVD (40% vs. 22%, $p < 0.0001$). Similar results have been reported by a Japanese group for a population of 417 patients with STEMI treated with primary PCI within 24 h from symptom onset [8]. The presence of CTO, (found in only 8% of patients), as in the previous analysis, was associated with a higher incidence of shock (25% vs. 11%, $p < 0.05$). Again, 30-day mortality rate was significantly higher in the CTO group (14.3% vs. 3.4%, $p < 0.01$). In the present population the presence CTO was found in 17% of all patients, and 33% of the MVD group. Knowing the results of previous studies, high-risk subjects were deliberately excluded to reduce the impact of other powerful predictors of mortality. Most likely that was the reason no independent effect of CTO could bedemonstrated on in-hospital and 30-day mortality, although among patients with MVD 30-day mortality rate in the CTO group was almost twice as high as those without CTO (6.8% vs. 3.8%, $p = 0.167$). Studies that also included patients in cardiogenic shock reported significantly higher early mortality in CTO group [7, 8]. In this study however, each subsequent observation period the significance of CTO as a predictor grew, and after 1 year cardiac mortality was significantly higher in this group (15.1% vs. 7.6%, $p = 0.015$). Since then, the presence of CTO became an independent risk factor of mortality, with a much

stronger impact on survival than the mere presence of MVD, which no longer played an independent role in patient outcome.

This raises the question about the possible mechanisms responsible for a poorer prognosis of patients with STEMI and concomitant presence of CTO. In the acute phase of STEMI the lack of sufficient collateral circulation to the IRA from the donor vessel being chronically occluded may play a significant role. This explains the higher incidence of cardiogenic shock in this group of patients, described in the above-cited papers [6, 7]. In addition, as demonstrated in the present group, CTO patients are more likely to have a history of previous MI, hence poorer left ventricular function, which is one of the major predictors of poor prognosis [8, 9]. Moreover, prior to the index MI, IRA might have been a donor artery of collateral circulation to the myocardium supplied by the CTO vessel. Even after successful primary PCI, due to the damage of microvascular circulation, the collateral flow to this area may be permanently impaired [9, 10]. The question remains whether the results of this and other studies justify routine treatment aimed at complete revascularization, including the opening of chronically occluded arteries in STEMI patients. Since the current guidelines were released, the PRAMI and CvLPRIT trials have shown improved outcomes with a comprehensive approach [11, 12]. This question is even more problematic regarding CTO lesions. During the 80s and 90s of the last century, due to the limited success rate of PCI procedures, majority of CTO lesions were left untreated or alternatively patients with MVD were referred to CABG. In recent years, owing to major developments in PCI techniques, significant improvement in outcomes of recanalization procedures has been observed. In experienced centres the reported success rate is close to 90% [13, 14]. Multiple studies support the benefit of opening a CTO with regard to symptom relief [15]. Recovery of left ventricular function has also been reported, but this effect strongly depends on the presence of viable myocardium [16, 17]. Finally, increasingly more studies provide data on the role of CTO as an predictor of sudden cardiac death, and long-term mortality [18]. In a recent meta-analysis of 23 observational studies, Khan et al. [19]. found that successful recanalization of a CTO resulted in improved all-cause mortality, and lower rates of major adverse cardiac events. One of the possible explanations may be the favourable antiarrhythmic effect of successful recanalization of CTO. In recently published paper Cetin et al. [20] demonstrated that after successful opening of the occluded vessel, ECG markers of ventricular repolarization inhomogeneity significantly improved, as compared with the pre-PCI values. Lee et al. [21] reported that in 60 out of 88 patients with CTO, in whom an attempt of PCI was made after the acute phase of MI, the procedure was successful in 40 (67%) patients. There were no deaths during follow-up in this successful group, while in patients in whom PCI failed or was not attempted death occurred in 23% ($p = 0.001$). Thus, it may be concluded that the results of thisstudy add one more premise to the general agreement that each STEMI patient with CTO in non-culprit vessel should be considered for future procedures to ensure completeness of revascularization. In the present study 155 patients with MVD underwent PCI of vessel other than an IRA (18.5%) during the first year. Unfortunately, accurate data on how many recanalization attempts were made and what was the outcome of these procedures was not available

Limitations of the study

A major limitation of the study is that it was a non-randomized, observational, single centre design. The study patients were treated many years ago with techniques not recommended under current guidelines. Only bare metal stents were implanted and no aspiration thrombectomy devices were used during procedures. Another limitation of the study is the lack of data on left ventricular function, both on admission and after discharge from the hospital. The angiograms were not reviewed by a central angiographic core lab. Not all of the endpoints could be assessed and confirmed by direct visits; some of them were obtained by telephone contact. We do not know how many PCI procedures performed during the observation time concerned CTO vessels, and what the success rate was.

Conclusions

The presence of CTO is an independent predictor of the long-term mortality in STEMI patients treated with primary PCI. The longer the observation time the more significant the impact of CTO has on survival.

The paper carries additional information on the importance of the presence of CTO in patients with coronary artery disease, and particularly with STEMI. In recent years, a major development in PCI techniques have been observed, especially regarding CTO procedures. This should prompt clinicians to carefully make evaluations of all

STEMI patients with regard to the indications of complete revascularization including chronically occluded vessels.

Conflict of interest: None declared

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