Periprocedural Myocardial Injury and Long-Term Clinical Outcome in Patients Undergoing Percutaneous Coronary Interventions of Coronary Chronic Total Occlusion

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ABSTRACT: Background. Periprocedural myocardial injury (PMI) after percutaneous coronary intervention (PCI) might occur more frequently during challenging procedures such as PCI of chronic coronary total occlusion (CTO). The prognostic implication of PMI in CTO-PCI remains unclear. **Methods.** From January 2006 to September 2012, a total of 715 consecutive patients undergoing CTO-PCI were screened at three centers. Only patients with available pre-PCI and post-PCI troponin (cTn) were included (n = 442). PMI was defined as an elevation of cTn >5x the upper reference limit (URL), or a rise of cTn >20% if baseline values were elevated. **Results.** Patients were grouped into: (1) successful CTO-PCI and no-PMI (Group A; n = 195); (2) successful CTO-PCI with PMI (Group B; n = 133); failed CTO-PCI (Group C; n = 114). Occurrence of major adverse cardiovascular event (MACE) was assessed in 431 patients (97%), at a median follow-up of 25 months, and were significantly lower in patients successfully treated without PMI occurrence, while increased in cases of PMI or failed CTO-PCI (Group A, 9%; Group B, 15%; Group C, 28%; hazard ratio, 1.57 (95% confidence interval, 1.12-2.18]; *P*<.01). At Kaplan-Meier analysis, MACE-free survival was significantly higher in Group A (log-rank, 21.46; *P*<.001). **Conclusion.** Successful CTO revascularization is still associated with a better long-term clinical outcome vs patients in whom it failed, regardless of the occurrence of PMI.

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Periprocedural myocardial injury (PMI) frequently occurs after percutaneous coronary interventions (PCI).[1] This has been associated with adverse cardiovascular outcomes, even in the absence of symptoms or electrocardiographic changes.[1-3] Nevertheless, the real clinical impact of PMI has been recently questioned, especially when small myocardial enzymatic leakage takes place.[4] Indeed, the mismatch between PMI and clinical outcome in some patients might be due to the fact that the enzymatic release reflects a more complex patient and coronary anatomy, rather than a true infarction able to impair myocardial function.[5-8]

Coronary chronic total occlusion (CTO) is often the marker of more severe and extensive atherosclerotic disease. CTOs represent the most challenging PCI procedure, but when successfully revascularized are associated with an improved long-term clinical outcome as compared with conservative therapy.[9-11] On the other hand, during CTO-PCI, PMI might commonly occur as a consequence of side-branch occlusion and thromboembolic complications secondary to extensive coronary manipulations.[12,13] However, it is still unclear whether the occurrence of PMI after a successful CTO-PCI might have a prognostic clinical impact that would jeopardize the expected clinical benefits derived from recanalization.

Methods

Study population. From January 2006 to September 2012, a total of 715 consecutive patients undergoing CTO-PCI in a major native coronary artery were retrospectively considered for inclusion at three centers (Cardiovascular Center Aalst OLV Hospital and Oost-Limburg Hospital, Belgium, Royal Brompton Hospital, United Kingdom). All patients had angina, viability, and/or reversible myocardial ischemia in the territory of the occluded artery. Patients with available pre-PCI and post-PCI troponin (cTn) were eventually included (n = 442). A *CTO* was defined as the complete obstruction of a native coronary artery with duration >3 months and Thrombolysis in Myocardial Infarction (TIMI) flow vessel grade 0. *Successful CTO procedure* was defined as coronary revascularization with final TIMI flow grade ≥2 and full coverage with stents of the occluded segment and residual stenoses <10%.[14] Patients presenting with a small size of the territory of distribution of the occluded artery (ie, small diagonal or marginal branches) were excluded. Values of troponins, creatinine, and hemoglobin at baseline and at 12-24 hours after the procedure were collected to detect possible occurrence of PMI, acute kidney injury, and major bleedings. The local ethics committees approved the use of clinical data for this study, and all patients provided written informed consent.

Table 1. Clinical characteristics.

	Group A (No PMI)	Group B (PMI)	Group C (Failed PCI)	*P*-Value	*P*-Value (Group A vs B)	*P*-Value (Group B vs C)
Number of patients	195 (44%)	133 (30%)	114 (25%)	–	–	–
Age (years) Range	64 (58-73)	64 (55-71)	70 (62-76)	<.001	NS	<.05
Male gender	153 (78%)	114 (86%)	91 (80%)	.24	.11	.24
Ejection fraction (%) Range	65 (54-74)	55 (50-60)	63 (54-71)	<.001	<.05	NS
Smoker	90 (45%)	53 (40%)	56 (48%)	.52	.36	.34
Hypertension	118 (60%)	79 (59%)	69 (60%)	.98	.91	.90
Hyperlipidemia	146 (75%)	100 (75%)	80 (70%)	.60	>.99	.39
Diabetes	39 (20%)	36 (27%)	28 (25%)	.31	.14	.66
Peripheral arterial disease	14 (7%)	13 (10%)	21 (18%)	.01	.42	.06
Chronic kidney disease	4 (2%)	2 (1%)	4 (3%)	.55	>.99	.42
Previous PCI	84 (43%)	56 (42%)	40 (35%)	.36	.91	.30
Previous CABG	34 (17%)	24 (18%)	25 (22%)	.60	.88	.52

Data provided as median (range) or number (percentage). CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; PMI = periprocedural myocardial injury.

Procedural protocol. CTO-PCI was performed via radial or femoral artery route with 6-8 Fr guiding catheters. All patients were treated with aspirin and clopidogrel before the procedure. Antegrade or retrograde approaches were used at operator discretion depending on the anatomy of the coronary artery, lesion morphology, and previous failed procedure(s). After successful CTO recanalization, coronary stenting was uniformly performed. During the procedure, heparin was administered and activated clotting time (ACT) was regularly maintained at ≥250-300 seconds. All patients with successful vessel revascularization received aspirin indefinitely and clopidogrel for at least 12 months post procedure. Quantitative coronary angiography was performed on end-diastolic frames before and after the procedure, using the computer-based analysis system Siemens QuantCor QCA (ACOM.PC 5.01; Siemens Medical Systems, Inc), based on the CAAS II system (Pie Medical Imaging).

Definitions and study endpoints. *PMI* was defined as an elevation of cTn >5x the 99th percentile upper reference limit (URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn >20% if baseline values were elevated.[15] The *primary study endpoint* was the cumulative incidence of *major adverse cardiovascular event (MACE)* at 2 years, defined as the composite of overall death, non-fatal myocardial infarction (MI) and *clinically-driven target-vessel revascularization (TVR)*, which was defined as any attempted percutaneous or surgical revascularization of the target vessel after the index procedure in the presence of recurrent angina or proven ischemia. Clinical follow-up was performed in all patients and collected through outpatient clinic evaluations, hospital records, or telephone interviews. Patient clinical outcomes were grouped as follows: (1) group A: successful CTO-PCI; (2) group B: successful CTO-PCI with PMI; (3) and group C: failed CTO-PCI.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation or median (interquartile range) as appropriate and compared using one-way ANOVA. Categorical data are presented as frequency (percentage) and were compared using Fisher's exact test or the Pearson χ^2 test. Normal distribution was assessed by the Kolmogorov-Smirnov test. Two-year cumulative MACE rates were estimated by the Kaplan-Meier method. The Cox proportional-hazards model was used to compare clinical outcomes between groups. A probability value of <.05 was considered significant; all tests were two-tailed. Logistic regression analysis was performed to identify the predictors of PMI. Data were analyzed with SPSS version 17.0 software (SPSS, Inc) and GraphPad Prism 5.00 (GraphPad Software, Inc).

Results

Clinical characteristics (Table 1). CTO-PCI was successful in 328 patients (74%): in 195 (44%; group A) with no PMI occurrence, and in 133 with associated PMI (30%; group B). CTO-PCI failed in 114 patients (25%; group C). PMI occurred in 44 patients (39%) of group C; nevertheless, these patients were pooled in the same group considering that no differences were observed in the clinical events up to 24 months as compared with group C patients without PMI (Supplementary Table 1; see www.invasivecardiology.com). The three groups significantly differed in terms of age, left ventricular ejection fraction (EF), and prevalence of peripheral artery disease (PAD). In addition, the EF of patients included in group A was significantly higher vs patients included in group B. This latter group included older patients as compared with group C. The enrollment period was particularly long, and PMI incidence decreased over the time (Supplementary Table 2; see www.invasivecardiology.com).

Table 2. Angiographic and procedural characteristics.

	Group A (No PMI)	Group B (PMI)	Group C (Failed PCI)	*P*-Value	*P*-Value (Group A vs B)	*P*-Value (Group B vs C)
Vessel disease				<.001	<.001	.26
Single	106 (54%)	46 (35%)	51 (45%)			
Double	64 (33%)	47 (35%)	33 (29%)			
Triple	25 (13%)	40 (30%)	30 (26%)			
Multivessel disease	89 (46%)	87 (65%)	63 (55%)	.01	<.001	.12
CTO target vessel				.54	.60	.27
Left anterior descending	54 (28%)	39 (29%)	25 (22%)			
Left circumflex	34 (17%)	28 (21%)	21 (18%)			
Right coronary artery	107 (55%)	66 (50%)	68 (60%)			
Successful first attempt	141 (86%)	96 (78%)	–	.09	.09	–
In-stent restenosis	18 (9%)	6 (4%)	6 (5%)	.19	.13	>.99
Rentrop grade ≥2	145 (75%)	57 (43%)	17 (33%)	<.001	<.001	.24
Retrograde approach	10 (5%)	28 (21%)	19 (17%)	<.001	<.001	.42
Multivessel PCI	29 (15%)	36 (27%)	25 (22%)	.02	.01	.38
Stents per patient (n) Confidence interval	2 (2-3)	2 (2-3)	–	–	.20	–
Drug-eluting stent	182 (93%)	128 (97%)	–	–	.20	–
Stent diameter (mm)	3.0 ± 0.4	3.0 ± 0.4	–	–	.66	–
Stent length (mm) Range	55 (33-74)	56 (33-76)	–	–	.87	–
X-ray time (minutes) Range	28 (19-44)	36 (22-54)	36 (23-60)	.01	<.05	NS
Contrast medium (mL) Range	320 (250-475)	300 (210-400)	300 (200-400)	.04	NS	NS
TIMI major bleedings	6 (3%)	0 (0%)	3 (3%)	.13	.08	.10
Acute kidney injury	2 (1%)	4 (3%)	4 (3%)	.29	.23	>.99

Data provided as median (range) or number (percentage). PCI = percutaneous coronary intervention.

Angiographic and procedural characteristics (Table 2). A significant difference was observed between the three groups in terms of number of diseased vessels and rate of multivessel PCI. Distribution of the CTO target vessel was similar between all groups. In addition, a retrograde approach was less frequently performed in group A vs the other two groups. Of note, a higher rate of well-developed retrograde filling of the CTO vessel was particularly observed in group A.

Clinical follow up. Follow-up was obtained in 431/442 patients (97%) at a median of 25 months (IQR, 10-37 months). Cumulative incidence of clinical endpoints is shown in Table 3. MACE rate was significantly lower in group A, while it progressively increased in cases of PMI or failed PCI (group A, 9%; group B, 15%; group C, 28%; hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.12-2.18; *P*<.01). This association was mainly driven by the higher TVR rate, and remained significant after adjustment for clinical and angiographic characteristics (HR, 1.55; 95% CI, 1.11-2.16; *P*=.01). The rate of death or non-fatal MI was numerically similar between groups B and C. Nevertheless, this composite endpoint was not different between group A and group B, while a statistically significant difference was found between group A and group C (Supplementary Table 3; see www.invasivecardiology.com). At the Kaplan-Meier analysis, MACE-free survival was significantly higher in groups A and B vs group C (log-rank, 21.46; *P*<.001) (Figure 1). Only a trend was found toward higher MACE rate in group B vs group A (HR, 0.56; 95% CI, 0.29-1.08; *P*=.08), although this was not confirmed after adjusting for clinical and angiographic characteristics (HR, 0.72; 95% CI, 0.37-1.43; *P*=.35). However, MACE rate was significantly higher in group C vs group B (HR, 2.08; 95% CI, 1.18-3.67; *P*=.01); this difference was mainly driven by the higher TVR rate in group C, and it remained significant after adjusting for clinical characteristics (HR, 2.04; 95% CI, 1.14-3.64; *P*=.02).

Table 3. Clinical events at 24-month follow-up between the three patient groups.

	Group A (No PMI)	Group B (PMI)	Group C (Failed PCI)	Unadjusted HR (95% CI)	*P*-Value	Adjusted HR (95% CI)	*P*-Value
Death	3 (2%)	6 (4%)	9 (8%)	1.53 (1.82-2.88)	.18		
Target-vessel revascularization	12 (6%)	11 (8%)	23 (20%)	1.91 (1.27-2.88)	.01		
rePCI	8 (4%)	5 (4%)	11 (9%)				
CABG	4 (2%)	6 (4%)	12 (11%)				
Non-fatal myocardial infarction	1 (1%)	5 (4%)	3 (3%)	0.74 (0.30-1.83)	.52		
Death/non-fatal MI	4 (2%)	11 (8%)	10 (9%)	1.05 (0.62-1.78)	.85		
Major adverse cardiovascular event	16 (9%)	20 (15%)	30 (28%)	1.57 (1.12-2.18)	.01	1.55 (1.11-2.16)*	.01

*Adjusted for age, ejection fraction, peripheral arterial disease, multivessel percutaneous coronary intervention.
Data provided as number (percentage). HR = hazard ratio; CI = confidence interval. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention; PMI = periprocedural myocardial injury.

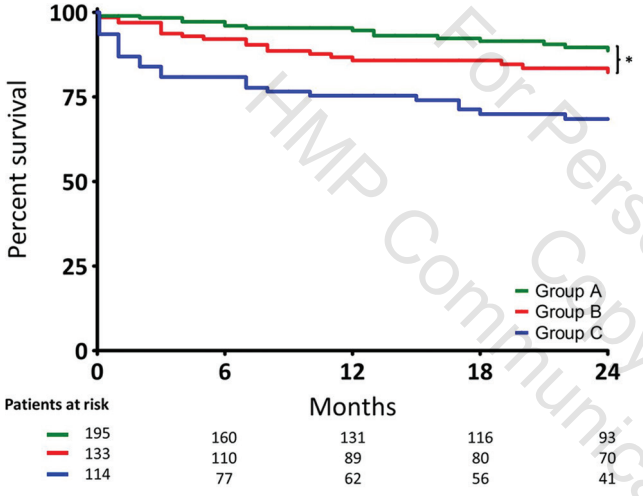

FIGURE 1. Major adverse cardiovascular events at 24 months.

Table 4. Multivariable analysis for predictors of periprocedural myocardial injury.

	OR	95% CI	*P*
Multivessel PCI	1.91	(0.99-3.33)	<.001
Retrograde approach	5.06	(2.26-11.34)	<.001
Rentrop collateral grade ≥2	0.27	(0.16-0.44)	<.001

CI = confidence interval; PCI = percutaneous coronary intervention.

Successful revascularization after the index CTO-PCI was eventually achieved in 28 patients (15%) in group A, 15 patients (11%) in group B, and 16 patients (15%) in group C (*P*=.70).

Predictors of PMI. Multivessel PCI at the time of the index CTO procedure and retrograde approach was significantly associated with the occurrence of PMI in our patients. On the contrary, the presence of well-developed retrograde collateral filling (Rentrop ≥2) of the target-vessel CTO was found to be protective (Table 4).

Discussion

Our findings demonstrate that compared with patients with failed CTO-PCI, a successful revascularization is associated with better long-term clinical outcome irrespective of the occurrence of PMI.

CTOs are the most complex and challenging coronary lesions for PCI, with a success rate that ranges from 55% to nearly 100% depending on the operator's experience.[16,17] Notably, successful CTO-PCI has been associated with an improved long-term clinical outcome vs patients with failed PCI, particularly in younger patients with both preserved EF and renal function.[18-20] The use of sophisticated techniques (like retrograde approach and antegrade dissection/reentry technique) and specific novel guidewires has significantly contributed to improved success rates in CTO even in high-risk patients with very complex coronary anatomies.[21,22] However, after adoption of the latter techniques, the incidence of PMI after CTO-PCI has increased.[23]

Recently, Lo et al showed that troponin was elevated more often than expected after CTO-PCI, although they found no significant association with MACE rate.[13] This could be related to the higher sensitivity of troponin in detecting even the smallest loss of viable myocardium with limited impact on clinical outcome. Alternatively, the troponin elevation could have only reflected the more complex coronary atherosclerotic disease of these patients, therefore diluting its prognostic value. Our results confirm and further extend this evidence. Indeed, patients who underwent successful CTO-PCIs with PMI showed only a trend toward a worse clinical outcome, as compared with patients who were likewise successfully treated with PCI but without PMI. These results are reassuring toward the use of more complex techniques. In fact, the related expectable higher risk of PMI, due to its limited clinical impact, might be largely offset by the long-term benefit deriving from the higher success rate of recanalization associated with these techniques.

Furthermore, in this study we found that well-developed retrograde collateral filling of the target CTO vessel protects against the occurrence of PMI. This can be explained by the fact that collaterals are able to prevent myocardial necrosis, and

may even uphold metabolic supply to the territory distal to an occlusion in order to maintain full contractile capacity.

Study limitations. Several limitations inherent to our retrospective study should be acknowledged, ie, event under-reporting, inability to account for operator decisions, short follow-up, low event rate (especially for death), and many other potential confounding factors including baseline clinical and procedural differences between the groups. These limitations remain, although we tried to minimize their impact by adjusting the Cox regression analysis to assess the clinical outcomes. Duration of CTO was certain (ie, angiographically confirmed) in nearly 70% of the patients, while it was likely (ie, clinically confirmed) in the remaining patients. Screen failure rate was 38%, mostly as a consequence of the lack of troponin before the procedure. The enrollment period was particularly long; therefore, the advantages due to technical improvements might have partially affected both the success rate and the incidence of PMI. The occurrence of PMI might represent a marker of the underlying atherosclerotic disease severity, therefore making these patients more susceptible to the occurrence of this complication.[24-26] Whether the clinical outcomes of patients with successful CTO-PCI complicated with PMI are mostly influenced by a more advanced atherosclerotic burden rather than by the loss of myocardial tissue is difficult to establish.

Conclusion

Successful revascularization of a coronary CTO is associated with a better long-term clinical outcome regardless of the occurrence of PMI.

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Supplementary Table 1. Breakdown of clinical events at 24-month follow-up in group C according to the occurrence of periprocedural myocardial injury.

	Group C (No PMI) (n = 70)	Group C (PMI) (n = 44)	*P*-Value
Death	8 (12%)	1 (2%)	.09
TVR	15 (22%)	8 (18%)	.81
Non-fatal MI	2 (3%)	1 (2%)	>.99
Death/non-fatal MI	8 (12%)	2 (4%)	.31
MACE	21 (32%)	9 (21%)	.28

TVR = target-vessel revascularization; MACE = major adverse cardiovascular events; MI = myocardial infarction.

Supplementary Table 2. Occurrence of periprocedural myocardial injury in function of the inclusion period.

	CTO Before February 5, 2008	February 5, 2008 < CTO < July 15, 2009	CTO After July 15, 2009	*P*-Value
	n = 145	n = 147	n = 150	
PMI overall	101 (70%)	43 (29%)	33 (22%)	<.01
PMI in successful procedures	80 (70%)	25 (25%)	28 (25%)	<.01

CTO = chronic total occlusion; PMI = periprocedural myocardial infarction.

Supplementary Table 3. Multivariable analysis for death or non-fatal myocardial infarction among the three groups.

	Death/Non-fatal MI	HR (95% CI)	*P*-Value
Group A	4 (2%)	Ref.	Ref.
Group B	11 (8%)	2.39 (0.74-7.67)	.14
Group C	10 (9%)	1.89 (1.04-3.42)	.04

MI = myocardial infarction; HR = hazard ratio. Adjusted for age, ejection fraction, peripheral arterial disease, and multivessel percutaneous coronary intervention.