Impact of periprocedural myocardial injury on long-term clinical outcomes of chronic total occlusion patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis
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Background: Several studies have evaluated the long-term clinical outcomes of periprocedural myocardial injury for chronic total occlusions patients. However, the results of these studies were inconsistent. To determine whether the periprocedural myocardial injury has adverse effects on long-term clinical outcomes in chronic total occlusion patients undergoing percutaneous coronary intervention.

Methods: We searched Cochrane Library, PubMed, and Embase for eligible articles from their date of inception up to March 2019. Long-term clinical outcomes included major adverse cardiac events, all-cause death, cardiac death, myocardial infarction, and target vessel revascularization. Odds ratios with 95% confidence intervals were calculated as summary statistics by using Review Manager software.

Results: A total of 8 observational studies involving 5879 chronic total occlusions patients were included in this meta-analysis. These results of this meta-analysis indicated that periprocedural myocardial injury was associated with a higher risk of major adverse cardiac events (odds ratio, 1.94; 95% confidence interval, 1.22–3.08; P = 0.005), a higher risk of all-cause death (odds ratio, 1.30; 95% confidence interval, 1.02–1.64; P = 0.03), a higher risk of cardiac death (odds ratio, 2.59; 95% confidence interval, 1.41–4.78; P = 0.002), a higher risk of myocardial infarction (odds ratio, 3.07; 95% confidence interval, 1.90–4.98; P < 0.00001), and a higher risk of target vessel revascularization (odds ratio, 2.07; 95% confidence interval, 1.35–3.16; P=0.0008) than non-periprocedural myocardial injury.

Conclusion: Periprocedural myocardial injury was associated with significantly increased risk of major adverse cardiac events, all-cause death, cardiac death, myocardial infarction, and target vessel revascularization in chronic total occlusion patients undergoing percutaneous coronary intervention at long-term follow-up.

Keywords: chronic total occlusion, meta-analysis, outcomes, percutaneous coronary intervention, periprocedural myocardial injury

Introduction
Percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) remains one of the most challenging percutaneous procedures owing to angiographic and procedural complexities, which is considered to be the final frontier of PCI for interventional cardiologists. However, the success rates of PCI for CTO lesion have improved over the last decade because of the development of novel devices and procedural techniques as well as accumulated operator experience [1,2]. Previous studies have demonstrated that a successful revascularization of CTO lesion was associated with better clinical outcomes compared to a failed procedure or conservative therapy [3–6]. Nevertheless, on the other hand, given the complex nature of the CTO-PCI procedure, periprocedural complications are unavoidable and jeopardize patient prognosis. Periprocedural myocardial injury (PMI) is one of the most common complications of CTO-PCI procedure.

PMI is a well-known complication of PCI procedures and is frequently observed in a considerable proportion of patients who underwent PCI procedure [7–9]. Previous studies have shown that PMI was associated with adverse clinical outcomes in unselected populations undergoing PCI [10–12]. However, based on the existing limited data, the clinical significance of PMI in CTO patients who underwent PCI remains controversial. Therefore, we performed this meta-analysis to systematically evaluate whether the occurrence of PMI has a negative impact on long-term prognosis in CTO-PCI patients.
Materials and methods

Search strategy
We searched Cochrane Library, PubMed, and EMBASE from their date of inception up to March 2019 for eligible trials. The following keywords were used: “chronic total occlusion or CTO” AND “periprocedural myocardial injury or periprocedural myocardial infarction or PMI”. In addition, to retrieve the most eligible studies, we also scanned the reference list of relevant reviews and manually searched relevant eligible studies. The language of relevant reviews was restricted to English.

Inclusion and exclusion criteria
Studies were eligible for inclusion in this meta-analysis if (1) they compared PMI with non-PMI in CTO patients who treated with PCI; (2) they reported at least one of the following outcomes: all-cause death, cardiac death, myocardial infarction (MI), target vessel revascularization (TVR), and major adverse cardiac events (MACEs); and (3) they were observational studies. The following studies were excluded from this meta-analysis: (1) studies which included non-CTO patients or CTO patients who not treated with PCI; (2) studies which lacked a control group; (3) studies which had no available outcomes even after the corresponding authors was contacted; and (4) case reports, abstracts, reviews, editorials, letters, meta-analysis, and duplicate publications.

Endpoints and definitions
The clinical outcomes of this meta-analysis included MACEs, all-cause death, cardiac death, MI, and TVR. The definition of MACEs and PMI was defined by each study. All-cause death was defined as death from any cause. Cardiac death was defined as death from cardiac origin. TVR was defined as repeated revascularization of the target vessel by PCI or coronary artery bypass grafting.

Data extraction and quality assessment
Two investigators (M.-J.L. and C.-F.C.) independently extracted the following data using a standardized form: name of first author, publication year, country, ethnicity, type of study, number of patients, baseline features of the subjects (mean age, percentage of males, diabetes mellitus, hypertension, dyslipidemia, previous MI, and previous PCI), CTO lesion location, definition of PMI, and median follow-up duration. Any disagreements about the extracted data were resolved by consensus. The quality of the included studies in the meta-analysis was assessed using the Newcastle–Ottawa Scale.

Statistical analysis
Odds ratios (OR) with 95% confidence interval (CI) were calculated as summary statistics. The heterogeneity between studies was calculated using Cochran Q test and I² statistic, which was considered significant when \( P < 0.10 \) in the Q test, or \( I^2 > 50\% \). The random-effects model (DerSimoniane-Laird method) was used to calculated the pooled ORs when the \( I^2 > 50\% \); otherwise, the fixed-effect model with the Mantel-Haenszel method was used when the \( I^2 < 50\% \). Subgroup analyses were performed according to the different ethnicity (Caucasian and Asian populations) to explore potential sources of heterogeneity. Sensitivity analyses were carried out by sequentially omitting each trial to verify the robustness of the overall results. All P-values were two-sided, and a P-value < 0.05 was considered statistically significant. All statistical analyses were conducted by using Review Manager 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark).

Results
Characteristics of the included studies
As shown in Fig. 1, a total of 8 trials [13–20] involving 5879 patients were included in the meta-analysis. All of these studies included in the meta-analysis were observational study. The main characteristics of each study were summarized in Tables 1 through 3. Of the 8 studies, two studies were carried out in Korea, two in China, one in Canada, one in European Union, one in Poland, and one in Germany. From the perspective of the ethnicity, four studies assessed Caucasian population and four assessed Asian population. Among the 8 studies, the PMI of 3 studies was defined by troponin, and the rest was defined by the creatine kinase MB (CK-MB). The sample size of studies varied from 337 to 1909 patients. Additionally, the median follow-up duration of studies varying from 1 year to 64.8 months.

Long-term clinical outcomes

Major adverse cardiac events
Seven studies reported the incidence of MACEs. PMI was associated with a significant increase in the risk of MACEs compared with non-PMI (absolute risk, 15.7% vs. 15.5%; OR, 1.94; 95% CI, 1.22–3.08; \( P < 0.00001 \)) (Fig. 2a).

All-cause death
Seven studies reported the incidence of all-cause death. PMI was significantly associated with increased the risk of all-cause death compared with Non-PMI (absolute risk, 11.7% vs. 9.1%; OR, 1.30; 95% CI, 1.02–1.64; \( P = 0.03 \)) (Fig. 2b).

Cardiac death
Five studies reported the incidence of cardiac death. PMI was associated with a higher risk of cardiac death compared with non-PMI (absolute risk, 4.3% vs. 2.6%; OR, 2.59; 95% CI, 1.41–4.78; \( P = 0.002 \)) (Fig. 2b).

Myocardial infarction
The incidence of MI was reported in seven studies. PMI can significantly increase the risk of MI compared with non-PMI (absolute risk, 5.2% vs. 3.5%; OR, 3.07; 95% CI, 1.90–4.98; \( P < 0.00001 \)) (Fig. 2b).
The incidence of TVR was reported in five studies. PMI was significantly associated with increased the risk of TVR compared with non-PMI (absolute risk, 9.1% vs. 4.0%; OR, 2.07; 95% CI, 1.35–3.16; \( P = 0.0008 \)) (Fig. 2b).

**Heterogeneity analysis**
As for MACEs, significant heterogeneity between studies included in the meta-analysis were observed (\( I^2 = 60\% \)). Therefore, subgroup analysis was performed to identify the sources of the heterogeneity observed across the studies. The result indicated that the heterogeneity was significantly decreased in Caucasian populations (\( I^2 = 0\% \)); however, the heterogeneity was still significant in Asian populations (\( I^2 = 70\% \)).

**Sensitivity analysis**
To evaluate the reliability of the results of this meta-analysis, sensitivity analysis was performed by omitting each individual study one by one to evaluate whether or not each study changed the results. The result of sensitivity analysis indicated that all these outcomes were reliable.

**Discussion**
The meta-analysis demonstrated that PMI was associated with significantly increased risk of MACEs, all-cause death, cardiac death, MI, and TVR in CTO patients undergoing PCI at long-term follow-up.

Previous several studies have shown that PMI following PCI was associated with worse adverse clinical events. Park *et al.* [21], found that PMI was associated
Fig. 2

(a) Comparison between PMI and non-PMI in the risk of major cardiac adverse events. (b) Comparison between PMI and non-PMI in the risk of all-cause death, cardiac death, myocardial infarction, and target vessel revascularization. PMI, periprocedural myocardial injury.
with increased the risk of mortality. Prasad et al. [22], showed that isolated minor elevation in cardiac troponin T (cTnT) was independently associated with increased the risk of long-term mortality. A meta-analysis conducted by Feldman et al. [23], demonstrated that an elevation of cTnT or cardiac troponin I (cTnI) after nonemergent PCI was predictive of an increase in long-term mortality as well as the composite adverse events of all-cause mortality/MI. However, these studies did not evaluate CTO patients. In a study conducted by Lee et al. [24], the result showed that PMI was associated with an increased risk of long-term mortality after successful CTO-PCI. Moreover, this association between PMI and adverse clinical events was not reversed due to diverse definitions of PMI. Furthermore, Lo et al. [25], reported that PMI was associated with worse subsequent clinical outcomes in CTO patients who treated with PCI during median 2.3 years follow-up.

The following mechanisms may explain this observation. First, studies showed that PMI was usually associated with procedural complications, such as side-branch occlusion, abrupt closure, distal embolization, disruption of collateral flow, or coronary dissection [11,21,26]. In addition, the MRI study indicated that about 20% of myocardial necrosis events were caused by micro-embolization not seen on angiography [27]. Thus, in the long-term, myocardial injury may impair left ventricular function and predispose to arrhythmias, resulting in increased the risk of adverse cardiovascular events. Second, patients with elevated cTnT or CK-MB were more likely to have more severe coronary artery disease, complex lesion morphology, congestive heart failure, peripheral vascular disease, and the need for more advanced coronary interventions. Therefore, an elevated cTnT or CK-MB represented the severity of coronary atherosclerosis lesions, and which has been proved to have a significant relationship with the worse prognosis [28,29]. Third, CK-MB and cTnI elevation after PCI may be a marker of the increased atherosclerotic plaque burden and inflammatory state [30,31]. Studies have showed that patients who received anti-inflammatory and antithrombotic drugs, such as statins and glycoprotein IIb/IIIa inhibitors, were associated with a lower incidence of myonecrosis after PCI and had better long-term clinical outcomes [32,33]. Fourth, patient characteristic such as drug resistance may be contributed to myocardial damage. Chen et al. [34], showed that patients with aspirin resistance were more likely to have a higher incidence of myonecrosis following nonurgent PCI and subsequently a worse outcome. However, further clinical trials are needed to investigate mechanisms linking myocardial injury to adverse clinical events.

Significant heterogeneity across studies was identified in terms of the endpoint of MACEs. Therefore, we conducted subgroup analysis according to the different ethnicity (Caucasian and Asian populations) to explore sources of heterogeneity. The result of heterogeneity analysis showed that heterogeneity was significantly decreased in Caucasian populations. Thus, ethnicity may

### Table 2 Main characteristics of studies included in this meta-analysis

| Study      | DM (%) PMI | Non-PMI | Hypertension (%) PMI | Non-PMI | Dyslipidemia (%) PMI | Non-PMI | Previous MI (%) PMI | Non-PMI | Previous PCI (%) PMI | Non-PMI |
|------------|------------|---------|----------------------|---------|----------------------|---------|---------------------|---------|----------------------|---------|
| Dautov     | 35         | 40      | 88                   | 79      | NA                   | NA      | 51                  | 58      | 67                   | 72      |
| Di Serafino | 27         | 20      | 59                   | 60      | 75                   | 75      | NA                  | NA      | 42                   | 43      |
| Jaguszewski | 19         | 25      | 82                   | 75      | 62                   | 57      | 64                  | 59      | 46                   | 47      |
| Jang       | 46         | 51      | 59                   | 64      | 32                   | 31      | 25                  | 21      | 24                   | 18      |
| Kim        | 35         | 40      | 83                   | 70      | 78                   | 85      | 13                  | 15      | NA                   | NA      |
| Toma       | 30         | 30      | 84                   | 82      | 85                   | 87      | 31                  | 23      | 24                   | 13      |
| Zhang      | 34         | 33      | 88                   | 92      | 41                   | 38      | 27                  | 25      | 10                   | 7       |
| Zhong      | 36         | 31      | 73                   | 64      | NA                   | NA      | 26                  | 31      | NA                   | NA      |

DM, diabetes mellitus; MI, myocardial injury; NA, not available; PCI, percutaneous coronary intervention; PMI, periprocedural myocardial injury.

### Table 3 Main characteristics of studies included in this meta-analysis

| Study      | LAD CTO (%) PMI | Non-PMI | LCx and OM CTO (%) PMI | Non-PMI | RCA CTO (%) PMI | Non-PMI |
|------------|-----------------|---------|------------------------|---------|-----------------|---------|
| Dautov     | 14              | 16      | 21                     | 20      | 58              | 57      |
| Di Serafino | 29              | 28      | 21                     | 17      | 50              | 55      |
| Jaguszewski | 21.2            | 32.5    | 21.2                   | 23.3    | 57.6            | 44.2    |
| Jang       | 43.2            | 43.1    | 27.1                   | 31.4    | 50              | 50.6    |
| Kim        | 43.5            | 44.6    | NA                     | NA      | NA              | NA      |
| Toma       | 26.7            | 28.1    | 22.9                   | 26      | 49.4            | 45.2    |
| Zhang      | 33.9            | 57.4    | 9.6                    | 11.1    | 56.5            | 31.9    |
| Zhong      | 42.5            | 47.1    | 10                     | 14      | 47.5            | 38.7    |

CK-MB, creatine kinase MB; CTO, chronic total occlusion; hTnT, high-sensitivity troponin T; LAD, left anterior descending; LCx, Left circumflex; NA, not available; OM, obtuse marginal; PMI, periprocedural myocardial injury; RCA, right coronary artery; TnT, troponin T; ULN, upper limit of normal; URL, upper reference limit.
be sources of the heterogeneity. Additionally, other factors, such as age, gender, length of follow-up, may also contributed to the heterogeneity across studies.

Our meta-analysis was the first study to systematically evaluate the clinical significance of PMI in CTO patients undergoing PCI, and the results of the analysis indicated that PMI was closely associated with adverse clinical outcomes. On the basis of the results of our study, we believed that routine cardiac marker measurement with cardiac enzymes or troponins following PCI should be necessary. At the same time, from the clinical point of view, these results suggested that it will be important to develop stricter strategies, including risk factor management of patients, careful selection of candidates, use of longer dual antiplatelet drugs and higher intensity statins, and more advanced interventional procedures, should be taken to reduce PMI occurrence and subsequently improving clinical outcomes.

**Limitations**

There were several limitations of this meta-analysis. First, this meta-analysis included only 9 non-randomized, observational studies. Thus, the results may be affected by confounding factors. Second, a total of 5879 patients was enrolled this meta-analysis and the small sample size may not be able to accurately evaluate the associations between PMI and clinical outcomes. Third, the definition of PMI varied among the included studies and may affect the reliability of the results. Fourth, some latest studies were included in our meta-analysis, so these studies were limited by follow-up time and may not deeply assess the relationship between PMI and outcomes.

**Conclusion**

PMI was associated with significantly increased risk of MACEs, all-cause death, cardiac death, MI, and TVR in CTO patients undergoing PCI at long-term follow-up.

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I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors.

**Conflicts of interest**

There are no conflicts of interest.

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