In-hospital outcomes of chronic total occlusion percutaneous coronary intervention in patients with and without prior coronary artery bypass graft

A systematic review and meta analysis

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Abstract
The clinical outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) in prior coronary artery bypass graft (pCABG) patients have been investigated; however, the results are inconsistent.

The present meta-analysis compared the clinical outcomes of CTO PCI patients with and without prior CABG (nCABG). The endpoints included technical success, procedural success, all-cause mortality, myocardial infarction (MI), major bleeding, coronary perforation, pericardial tamponade, emergency CABG, and vascular access complication.

A total of 7 studies comprising of 11099 patients were included in this meta-analysis. The results showed that compared to nCABG patients, pCABG patients were associated with lower technical success (82.3% versus 87.8%; OR, 0.60; 95% CI, 0.53–0.68; P < .00001; F = 0%) and procedural success (80.4% versus 86.2%; OR, 0.61; 95% CI, 0.53–0.70; P < .00001; F = 10%); a higher risk of all-cause mortality (OR, 2.95; 95% CI, 1.56–5.67; P = 0.0008; F = 0%), MI (OR, 2.30; 95% CI, 1.40–3.80; P = .001; F = 5%), and coronary perforation (OR, 2.16; 95% CI, 1.51–3.08; P < .00001; F = 52%). On the other hand, the risk of pericardial tamponade (OR, 0.42; 95% CI, 0.15–1.18; P = 0.10; F = 21%), major bleeding (OR, 1.51; 95% CI, 0.90–2.53; P = .11; F = 0%), vascular access complication (OR, 1.50; 95% CI, 0.93–2.41; P = 0.10; F = 0%), and emergency CABG (OR, 0.99; 95% CI, 0.25–3.91; P = .99; F = 0%) was similar in both groups.

Compared to nCABG patients, pCABG patients had lower CTO PCI success rates, higher rates of in-hospital mortality, MI, and coronary perforation, and similar risk of pericardial tamponade and vascular complication rates.

Abbreviations: CABG = coronary artery bypass graft, CTO = chronic total occlusion, MACE = major adverse cardiac events, MI = myocardial infarction, nCABG = without prior CABG, pCABG = prior CABG, PCI = percutaneous coronary intervention.

Keywords: chronic total occlusion, coronary artery bypass graft, meta-analysis, percutaneous coronary intervention

1. Introduction
Chronic total occlusion (CTO) is one of the most challenging coronary artery lesions identified in 20% of all coronary angiographies. The prevalence of CTO in patients with known coronary artery disease is between 30 to 50%. Owing to the complexity of percutaneous coronary intervention (PCI) for CTO, only 10% to 15% of all patients with CTO attempted to receive CTO-PCI revascularization. Over the past decade, dedicated equipment and revascularization techniques for the interventional treatment of CTO have advanced significantly, and remarkable progress has been achieved in CTO-PCI revascularization success rates. For example, Abdelmonem et al. found that compared to coronary angiography, multi-slice computed tomography had a higher sensitivity in identifying several CTO lesion characteristics. Benko et al. found that the SoundBite Crossing System, the first and only CTO device using a guidewire-like platform to deliver shockwaves to the point of vascular occlusion, had a stronger ability to pass through the CTO lesions as compared to the traditional guidewires. In addition, newer generation biodegradable polymer drug-eluting stents have improved device safety and efficacy as compared to the early-generation drug-eluting stents. Previous studies demonstrated that successful CTO PCI could significantly improve the quality of life and improve left ventricular function, and reduce long-term mortality and the risk of coronary artery bypass graft (CABG) surgery. Thus, successful revascularization by PCI has emerged as a promising alternative treatment for CTO lesions in the event of failed CABG.
Randomized controlled trials have shown that compared to PCI, CABG significantly improved the long-term clinical outcomes for the treatment of complex coronary lesions, such as multivessel coronary artery disease[9] and left main disease.[10] On the other hand, CABG itself can accelerate the development of atherosclerosis of native coronary arteries.[11] As a result, the prevalence of coronary artery CTO among coronary artery disease patients is much higher in patients with prior CABG (pCABG) than in those without prior CABG (nCABG).[11] Furthermore, pCABG patients exhibit complex coronary anatomy than nCABG patients, and repeat CABG was associated with worse long-term clinical outcomes as compared to initial CABG.[12] in this case, CTO PCI was preferred as revascularization strategy.

Some recent studies investigated the clinical outcomes of CTO-PCI in pCABG patients; however, the results were inconsistent. Some studies showed that pCABG patients had lower success rate but a similar overall risk for complications as compared to nCABG patients,[13-15] while other studies confirmed high success rate[16] and worse overall prognosis[17,18] between the 2 groups. Thus, whether the higher procedural complexity encountered during CTO-PCI in pCABG patients translated into poor clinical outcomes is yet to be clarified. The aim of this meta-analysis was therefore to compare success rate and in-hospital clinical outcomes of CTO-PCI in patients with and nCABG.

2. Material and methods

2.1. Literature search

Electronic databases including PubMed, Embase, and Cochrane Library were searched from inception to June 30, 2019. The following search terms were used: “chronic total occlusion,” “CTO,” “percutaneous coronary intervention,” “PCI,” “coronary artery bypass,” “coronary bypass,” “bypass surgery,” and “CABG.” The reference lists of the identified studies were screened for other potentially eligible studies. Our search was limited to the English language.

2.2. Inclusion and exclusion criteria

The studies satisfying the following criteria were considered for inclusion in the current meta-analysis:

(1) studies with CTO PCI patients;
(2) studies with comparisons of CTO PCI in patients with and nCABG;
(3) studies that reported incidences of in-hospital clinical outcomes in both groups; and
(4) observational studies.

The following studies were excluded from the meta-analysis:

(1) lacking a control group;
(2) without available original data;
(3) not published in the English language;
(4) duplicate publications; and
(5) abstracts, reviews, letters, notes, case reports, commentaries, and editorials.

2.3. Endpoints and definitions

The outcomes of the current study included technical success, procedural success, all-cause mortality, myocardial infarction (MI), major bleeding, coronary perforation, pericardial tamponade, emergency CABG, and vascular access complication. Technical success was defined as residual stenosis < 30% or < 50% with Thrombolysis in MI antegrade flow grade 3. Procedural success was defined as the achievement of technical success without in-hospital major adverse cardiac events (MACE). Major bleeding was defined as bleeding requiring transfusion, vasopressors, surgery or percutaneous intervention.

2.4. Data extraction and quality assessment

Two investigators (Mei-Jun Liu and Chao-Feng Chen) independently extracted the following data from the included studies: study characteristics, patients’ characteristics, angiographic characteristics, procedural characteristics, and outcomes of interest. Any disagreements about the extracted data were resolved by consensus or a third author adjudication. The Newcastle–Ottawa Scale was used to assess the quality of studies included in the meta-analysis.

2.5. Statistical analysis

Due to wide clinical and methodological variability across the trials, the random-effects model with the Mantel-Haenszel method was applied to calculate the pooled odds ratio (OR) with the 95% confidence interval (CI). The heterogeneity between the studies was assessed via a standard chi square test with significance set at $P < .10$ and assessed by means of $I^2$ statistic. A value of $I^2 > 50\%$ was considered as significant heterogeneity.[19] Subgroup analysis was performed to explore the sources of heterogeneity based on the publication year (before 2014 and after 2014). Sensitivity analyses were performed by sequential removal of the studies to evaluate the influence of each study on the overall effect. All $P$ values were two sided, and values of $P < .05$ were considered statistically significant. All statistical analyses were conducted using Review Manager 5.3 version (RevMan, The Cochrane Collaboration, Copenhagen, Denmark).

2.6. Ethics

Ethical committee or medical institutional board approval was not required for systematic reviews and meta-analyses

3. Results

3.1. Characteristics of the included studies

Fig. 1 shows the flowchart of the study selection. As a result, a total of seven observational studies[13-18,20] with 11099 patients (11512 lesions) were included in the current meta-analysis. The baseline characteristics of the studies included in this meta-analysis are summarized in Tables 1–3. The pCABG group included 2806 patients (2879 lesions), whereas the nCABG group included 8293 patients (8633 lesions). Four studies only reported in-hospital outcomes, and the remaining studies reported in-hospital and long-term outcomes. The included studies were published between 2013 and 2019. The sample size of the included studies ranged from 470 to 3418. The results of newcastle–ottawa scale quality assessment varied from 7 to 8.

3.2. Primary endpoints

The pCABG was associated with lower technical success (82.3% vs 87.8%; OR, 0.60; 95% CI, 0.53–0.68; $P < .00001$; $I^2 = 0\%$)
and procedural success (80.4% vs 86.2%; OR, 0.61; 95% CI, 0.53–0.70; \( P < .0001; I^2 = 10\% \)) as compared to nCABG (Fig. 2).

### 3.3. In-hospital secondary endpoints

Compared to nCABG, pCABG was associated with a higher risk of all-cause mortality (OR, 2.95; 95% CI, 1.56–5.57; \( P = .0008; I^2 = 0\% \)), MI (OR, 2.30; 95% CI, 1.40–3.80; \( P = .001; I^2 = 5\% \)), and coronary perforation (OR, 2.16; 95% CI, 1.51–3.08; \( P < .0001; I^2 = 52\% \)) (Fig. 3). However, no significant difference was observed in the risk of pericardial tamponade between pCABG patients and nCABG patients (OR, 0.42; 95% CI, 0.15–1.18; \( P = .10; I^2 = 21\% \)) (Fig. 3). Furthermore, the pCABG and nCABG patients were associated with a similar risk of major bleeding (OR, 1.51; 95% CI, 0.90–2.53; \( P = .11; I^2 = 0\% \)), vascular access complication (OR, 1.50; 95% CI, 0.93–2.41; \( P = .10; I^2 = 0\% \)), and emergency CABG (OR, 0.99; 95% CI, 0.25–3.91; \( P = .99; I^2 = 0\% \)) (Fig. 3).

### 3.4. Heterogeneity analysis

Significant heterogeneity among the studies was observed regarding coronary perforation (\( I^2 = 52\% \)). Thus, we performed subgroup analysis to explore the sources of heterogeneity with respect to the publication year (before 2014 and after 2014) and found significant heterogeneity in studies published before 2014, but none in those published after 2014.

### 3.5. Sensitivity analysis

Sensitivity analysis was conducted to evaluate the robustness of the results of the meta-analysis. It was observed that the results did not change significantly, and hence, could be deemed stable and reliable. However, with respect to the endpoint of pericardial tamponade, we found that when the study by Toma et al was removed, the result significantly changed (OR, 0.25; 95% CI, 0.08–0.77; \( P = .02; I^2 = 0\% \)), indicating that it was not sufficiently reliable and further studies are essential to investigate the correlation between the 2 groups.

### Table 1

The baseline characteristics of studies included in this meta-analysis.

| Study            | Yr    | Country              | Type of study   | Sample size (n) | No. of patients (n) pCABG/ nCABG | Follow-up     | NOS |
|------------------|-------|----------------------|-----------------|-----------------|----------------------------------|---------------|-----|
| Azzalini et al   | 2018  | North American, European, Japan | Observational   | 2058            | 401/1657                        | In-hospital 377 d | 8   |
| Christopoulos et al | 2014 | American             | Observational   | 496             | 176/320                         | In-hospital    | 7   |
| Dautov et al     | 2016  | Canada               | Observational   | 470             | 175/295                         | In-hospital 1 yr | 7   |
| Michael et al    | 2013  | American             | Observational   | 1363            | 508/655                         | In-hospital    | 7   |
| Tajti et al      | 2019  | American, European, Russian | Observational   | 3418            | 1101/2317                        | In-hospital    | 7   |
| Teramoto et al   | 2014  | Japan                | Observational   | 1292            | 153/1159                        | In-hospital    | 8   |
| Toma et al       | 2016  | Germany              | Observational   | 2002            | 202/1710                        | In-hospital 2.6 yr | 7   |

CABG = coronary artery bypass graft; nCABG = without prior CABG; NOS = Newcastle–Ottawa Scale; pCABG = prior CABG.
4. Discussion

To the best of our knowledge, the current study was the first meta-analysis to investigate the clinical outcomes of CTO PCI in pCABG patients. The results of this meta-analysis demonstrated that compared to nCABG patients, pCABG patients had lower technical and procedural success rates, higher rates of in-hospital mortality and MI, and similar major complication rates. Moreover, pCABG patients showed a higher risk of coronary perforation but similar risk of pericardial tamponade as compared to nCABG patients.

Several registries showed that the proportion of pCABG patients was higher in failed CTO PCI patients than that in successful patients, thereby indicating that pCABG was associat-

| Table 2 | The baseline characteristics of patients included in this meta-analysis. |
|---------|---------------------------------------------------------------|
| Study   | Age (yr) | Male n(%) | Hypertension n(%) | Diabetes mellitus n (%) | Dyslipidemia n (%) | Previous MI n (%) | Previous PCI n (%) |
| Azzalini et al | pCABG 69.2±8.0 | 366 (92%) | 345 (87%) | 191 (48%) | 362 (91%) | 219 (56%) | 291 (73%) |
|         | nCABG 64.3±10.6 | 1444 (87%) | 1215 (74%) | 579 (35%) | 1285 (78%) | 700 (43%) | 961 (58%) |
| Christopoulos et al | pCABG 68±9 | 158 (90%) | 164 (93%) | 86 (49%) | 17 (97%) | 77 (44%) | 116 (66%) |
|         | nCABG 64±10 | 272 (85%) | 285 (89%) | 122 (38%) | 298 (93%) | 102 (32%) | 182 (57%) |
| Dautov et al | pCABG 70±7 | 150 (86%) | 156 (93%) | 87 (52%) | NA | 105 (65%) | 133 (76%) |
|         | nCABG 64±11 | 226 (77.0%) | 217 (73%) | 86 (30%) | NA | 147 (51%) | 197 (67%) |
| Michael et al | pCABG 67.7±9.0 | 438 (86.2%) | 470 (92.6%) | 225 (44.3%) | 488 (96.0%) | 228 (44.9%) | 220 (43.4%) |
|         | nCABG 63.3±10.4 | 722 (84.4%) | 746 (87.2%) | 315 (36.8%) | 792 (92.6%) | 340 (39.8%) | 349 (40.8%) |
| Tajti et al | pCABG 67.3±9.3 | 959 (87.1%) | 1032 (93.7%) | 537 (48.8%) | 1049 (95.3%) | 621 (56.4%) | 810 (73.6%) |
|         | nCABG 63.2±10 | 272 (85%) | 285 (89%) | 122 (38%) | 298 (93%) | 102 (32%) | 182 (57%) |
| Teramoto et al | pCABG 68.2±8.2 | 125 (82%) | 91 (59%) | 65 (42%) | 54 (35%) | NA | NA |
|         | nCABG 66.0±8.2 | 932 (82%) | 690 (61%) | 427 (37%) | 423 (37%) | NA | NA |
| Toma et al | pCABG 68±9 | 257 (88%) | 26 (90%) | 113 (39%) | 265 (91%) | 139 (48%) | 88 (23%) |
|         | nCABG 65±11 | 1413 (83%) | 1385 (81%) | 477 (28%) | 1461 (63%) | 354 (21%) | 242 (14%) |

CABG: coronary artery bypass graft, MI: myocardial infarction, NA: not available, nCABG: without prior CABG, pCABG: prior CABG; PCI: percutaneous coronary intervention.

| Table 3 | The angiographic and procedural characteristics of studies included in this meta-analysis. |
|---------|---------------------------------------------------------------|
| Study   | RCA CTO vessel n (%) | LAD CTO vessel n (%) | LCX CTO vessel n (%) | Antegrade wire escalation n (%) | Antegrade dissection and re-entry n (%) | Retrograde approach n (%) |
| Azzalini et al | pCABG 210 (53%) | 83 (21%) | 102 (26%) | 135 (40%) | 66 (20%) | 133 (40%) |
|         | nCABG 816 (49%) | 515 (31%) | 322 (20%) | 921 (62%) | 228 (15%) | 330 (22%) |
| Christopoulos et al | pCABG 111 (63%) | 23 (13%) | 32 (18%) | 40 (23%) | 40 (23%) | 69 (39%) |
|         | nCABG 192 (60%) | 77 (24%) | 32 (10%) | 138 (43%) | 83 (26%) | 77 (24%) |
| Dautov et al | pCABG 83 (48%) | 18 (10%) | 51 (29%) | 45 (27%) | 37 (22%) | 83 (50%) |
|         | nCABG 182 (62%) | 55 (19%) | 45 (15%) | 115 (41%) | 63 (23%) | 102 (36%) |
| Michael et al | pCABG 285 (56.2%) | 72 (14.2%) | 139 (27.4%) | 479 (94.2%) | 149 (29.4%) | 237 (46.7%) |
|         | nCABG 468 (54.7%) | 214 (25.0%) | 172 (20.1%) | 834 (97.5%) | 245 (26.7%) | 232 (27.1%) |
| Tajti et al. | pCABG 630 (56.2%) | 186 (16.6%) | 293 (27.8%) | 744 (66.4%) | 94 (8.4%) | 282 (25.2%) |
|         | nCABG 1303 (55.1%) | 657 (27.8%) | 396 (16.7%) | 1935 (81.8%) | 175 (7.4%) | 255 (10.8%) |
| Teramoto et al | pCABG 93 (45%) | 45 (22%) | 64 (31%) | NA | NA | NA |
|         | nCABG 616 (43%) | 488 (34%) | 323 (22%) | NA | NA | NA |
| Toma et al | pCABG 128 (44%) | 43 (15%) | 107 (37%) | NA | NA | 122 (42%) |
|         | nCABG 803 (47%) | 513 (30%) | 393 (23%) | NA | NA | 354 (21%) |

CABG = coronary artery bypass graft, CTO = chronic total occlusion, LAD = left anterior descending artery, LCX = left circumflex artery; NA: not available, nCABG = without prior CABG, pCABG = prior CABG; PCI: percutaneous coronary intervention.
ed with a low possibility of CTO PCI procedural success.\textsuperscript{[21–23]} This phenomenon could be attributed to the following reasons: First, pCABG patients are at high risk. Compared to nCABG, patients with pCABG were older, more male, had more comorbidities, and had higher angiographic complexity.\textsuperscript{[21,24]} which makes CTO PCI more technically challenging in such patients. Second, CABG accelerated the progression of native coronary artery atherosclerosis. CTO of pCABG patients was characterized by severe calcification, moderate negative remodeling, and small necrotic core area. These differences in pathology along with abrupt and tapering pattern of proximal and distal lumens, which may exert a negative impact on the success rates of CTO PCI in such patients, might explain the differences in the success rates of CTO PCI in patients with and nCABG.\textsuperscript{[25]} Third, CABG leads to distortion, displacement, and deformation of the native coronary artery hindering CTO crossing attempts, which elevates the technical difficulty and decreases the success rate of CTO PCI. CTO PCI pCABG patients show a severe tortuosity and blunt stump, and tortuosity was considered to be a negative independent predictor of successful CT PCI. Fourth, complications during CTO PCI procedures might exert a negative impact on its success rate. For example, coronary perforation has been proved to be associated with lower technical and procedural success rates and high risk of periprocedural MACE.\textsuperscript{[26]}

Therefore, further improvement of devices and techniques that are used to optimize the outcomes of CTO PCI in these patients is necessary. The antegrade approach, especially antegrade wire escalation, is the hallmark of CTO PCI.\textsuperscript{[27]} During the last decade, the development of new dedicated guidewires and improvements in microcatheter design have improved the success rate of CTO PCI, the antegrade approach has significantly evolved, some operators suggested that antegrade dissection re-entry could be recommended as the initial crossing strategy. Some studies showed that antegrade dissection re-entry was associated with similar high success rates and low MACE risk as compared to antegrade wire escalation, especially for anatomically complex lesions and after a failure of other strategies.\textsuperscript{[28,29]} In this setting, the combined use of CrossBoss microcatheter and Stingray system was recommended since it was associated with a low risk of MACE after CTO PCI revascularization.\textsuperscript{[30]} Moreover, the CrossBoss catheter should be considered as the first-line device for in-stent CTO recanalization.\textsuperscript{[31]} Although the retrograde approach can improve the success rate of CTO PCI, the selection of interventional collaterals is also a key factor affecting the retrograde CTO PCI success rate. Saphenous vein grafts are effective conduits for retrograde CTO PCI in pCABG patients. Compared to other collaterals, the use of Saphenous vein grafts is associated with high technical success and low complication rates.\textsuperscript{[32]} Finally, the application of the hybrid approach can achieve overall success rates of 90% to 95% in real world practice with a low complication rate,\textsuperscript{[33,34]} thereby supporting its use for treating these patients.

Planning and meticulous preparation of the CTO PCI procedure is a key contributor to achieving success in revascularization. The scoring models not only quantitatively measure the difficulty and the probability of CTO PCI revascularization success but also objectively evaluate the anatomic and clinical complexity, which can aid the physicians in making optimal clinical decisions for each CTO patient. The J-CTO (multicenter CTO registry in Japan) score is currently the most widely used score predicting successful guidewire crossing through native coronary CTO lesions within 30 minutes.\textsuperscript{[33]} However, the J-CTO score failed to predict the final procedural success that used the hybrid approach. Conversely, the PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) score used final technical success as the primary endpoint, which is suitable for predicting the technical success in CTO PCI performed using the hybrid approach.\textsuperscript{[36]} Importantly, the PROGRESS CTO score has a predictive value for long-term outcomes in CTO PCI.

![Figure 2. Forest plot of technical success and procedural success. pCABG: with prior CABG; nCABG: without prior CABG; CABG: coronary artery bypass graft.](image-url)
Figure 3. Forest plot of all-cause mortality, myocardial infarction, coronary perforation, pericardial tamponade, major bleeding, vascular access complication, and emergency CABG. pCABG: with prior CABG; nCABG: without prior CABG; CABG: coronary artery bypass graft.
patients. The RECHARGE (REgistry of CrossBoss and Hybrid procedures in FrAnce, the NetherLands, BelGium, and UnitEd Kingdom) score is a novel, promising tool to assess the risk for technical failure in hybrid CTO PCI. Additionally, the RECHARGE score has been shown to be an independent predictor of long-term adverse outcomes. The CL score (Clinical and Lesion-related score) was superior to the J-CTO score in identifying CTO lesions and predicting the final successful CTO PCI revascularization. Moreover, the CL score seems to be a helpful tool for identifying the appropriate antegrade operators. I believe that in the current era of CTO PCI, we would benefit from the new CTO score. The new scoring model can not only predict the success and failure of CTO PCI procedure but also improve its efficiency and suggest the potential success of a specific strategy.

In accordance with a previous study, the current study showed frequent coronary perforation occurring in CTO PCI patients. However, the risk of cardiac tamponade among the 2 groups was similar. This phenomenon may be attributed to the potential protective effect of pericardial adhesion in pCABG patients, which obliterates the pericardial space and reduces the risk of cardiac tamponade. However, these data seem to promote the unpredictability of the risk of complications caused by cardiac tamponade. Notably, coronary perforation leads to fatal complications, such as local hematoma, which compresses various cardiac chambers and causes hemodynamic abnormalities, several studies have shown that coronary perforation was strongly associated with poor clinical outcomes. Thus, early treatment of coronary perforation in such patients is essential.

Strikingly, significant heterogeneity across the trials was observed with respect to coronary perforation. Subgroup analysis was performed to explore the sources of heterogeneity, and significant heterogeneity was observed in studies published before 2014, but none in those published after 2014. Thus, the publication year may have been source of heterogeneity. One potential reason could be that new CTO PCI technology, stents, and drugs have been developed rapidly, which might increase the variability among the studies. Other confounding factors, such as age, CTO lesion length, and number of stents, may also increase the heterogeneity among the studies.

5. Limitations

Nevertheless, the present study has several limitations. First, all studies included in our meta-analysis were observational with all the inherent limitations. Second, other confounding factors may have an impact on the outcome measures. Third, the definition of CTO differed among studies, and hence, the results may be variable. Fourth, the current study only reported the in-hospital procedural outcomes without examining the subsequent long-term clinical outcomes between CTO PCI patients with and nCABG. Fifth, some clinical endpoints only included a small number of studies, which might affect the statistical results.

6. Conclusions

Compared to the nCABG patients, pCABG patients had lower CTO PCI success rates, higher rates of in-hospital mortality, MI, and coronary perforation, and similar risk of pericardial tamponade and complication rates. Thus, further improvement of devices and techniques is essential to optimize the outcomes of CTO PCI in such patients.
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