



Review Article

Percutaneous coronary intervention provided better long term results than optimal medical therapy alone in patients with chronic total occlusion: A meta-analysis[☆]



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ABSTRACT

Aims: Studies comparing the outcome of percutaneous coronary intervention (PCI) along with optimal medical therapy (OMT) versus OMT alone in treatment of chronic total occlusion (CTO) are limited by observational design, variable follow-up period, diverse clinical outcomes, high drop-out and cross-over rates. This study aims to conduct a meta-analysis of published data of observational as well as randomized studies comparing long term outcomes of PCI+OMT versus OMT alone.

Methods and results: PubMed, Embase and Cochrane databases were systematically reviewed. 15 studies meeting criteria were included in the meta-analysis. The New-castle Ottawa scale was used to appraise the overall quality of the studies. Random-effects model with inverse variance method was undertaken. Major adverse cardiovascular events (MACE) which comprises of cardiac death, myocardial infarction, stroke, and un-planned revascularization were significantly lower in the PCI+OMT group (RR:0.76; 95% CI:0.61 to 0.95; $P < 0.00001$; $I^2 = 85\%$). All-cause mortality and cardiac death were significantly lower in the PCI+OMT group ($P < 0.00001$ in both). Myocardial infarction and stroke rates were lower in the PCI+OMT group, however they did not reach statistical significance ($P = 0.24$, $P = 0.15$ respectively). Unplanned revascularizations (of any vessel) were also similar in both the groups ($P = 0.78$, $I^2 = 88\%$). **Conclusion:** PCI of CTO is rewarded with better long term outcome, in terms of MACE, all-cause mortality and cardiac death with similar rates of un-planned revascularization.

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Abbreviations: ACEF, Age, Creatinine, and Ejection Fraction; CKD, Chronic Kidney Disease; CTO, Chronic Total Occlusions; CABG, Coronary Artery Bypass Grafting; LAD, Left Anterior Descending Artery; LCX, Left Circumflex Artery; LVEF, Left Ventricular Ejection Fraction; LOE, Level of Evidence; MACE, Major Adverse Cardiovascular Events; MD, Mean Differences; MVD, Multi-vessel Disease; OR, Odds Ratio; OMT, Optimal Medical Therapy; PCI, Percutaneous Coronary Intervention; PICO, Patient Intervention Comparator Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, Risk Ratios; RCA, Right Coronary Artery; SD, Standard Deviation; TIMI, Thrombolysis in Myocardial Infarction.

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1. Introduction

Chronic total occlusions (CTO) of the coronary arteries are defined as Thrombolysis in Myocardial Infarction (TIMI) zero flow for at least 3-months duration.¹ On coronary angiography, CTO is observed in approximately 16% of the patients with significant coronary artery disease.² Of this, two-third of the patients are treated with optimal medical therapy (OMT) and one-third of patients are referred for revascularization, of which merely 10% patients are referred for percutaneous coronary intervention (PCI).³

PCI of CTO is one of the biggest challenges in interventional cardiology. However, success rates for CTO PCI have improved with advances in technology and techniques with low risk of procedural complications. CTO-PCI can provide significant clinical benefits which include improvement in quality of life and angina.^{4–6} A meta-analysis by Hoebbers, et al. reported that successful CTO PCI resulted in an increase in left ventricular (LV) ejection fraction and a reduction in LV end-diastolic volume in comparison to OMT alone.⁷

Randomized controlled trials comparing outcome of PCI vs OMT in patients of CTO are few and the patient cohorts were very different. The results of the landmark studies have also been diverse, for example, EuroCTO trial met the primary endpoints but DECISION CTO study failed to reach the primary endpoints. Moreover, EuroCTO trials had a cross over rate of 7.2% in one year (17.5% in three years) and DECISION CTO trial reported almost 20% cross-over rate in three years' follow-up.^{4,5} Likewise, the observational studies are also limited by small sample sizes, variable follow-up periods, diverse clinical outcomes and unmatched patient-selections. Previous meta-analyses on the present context were restricted to studies with propensity-matched analysis and only reported the pooled hazard ratio and often did not separately report outcomes of PCI and coronary artery bypass grafting (CABG) in comparison to OMT.^{8–10} To overcome the lacunae of evidence, we reported the first meta-analysis incorporating both randomized and observational studies.¹¹ The aim of the present study was to conduct a meta-analysis of published data of observational as well as randomized studies comparing long term outcomes of PCI with OMT versus OMT alone in patients with CTO ([Online supplemental material, Supplement 1, PICO strategy](#)).

2. Methodology

The methodology of the study is depicted in [Fig. 1](#). This review was registered with PROSPERO (ID# 140110) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines ([Online supplemental material, Supplement 2, PRISMA checklist](#)).

2.1. Search strategy

A systematic review was conducted through Cochrane Controlled Trials Registry (CENTRAL), PubMed, and Embase databases for published articles from the year 2000 to present by searching for the key words, “chronic total occlusion” OR “chronic occlusion” AND “Angioplasty” AND “Stent” AND “Revascularization” AND “PCI” OR “Coronary intervention” AND “Optimal medical therapy” OR “Medical therapy” ([Online supplemental material, Supplement 3, search strategy](#)). To identify additional studies, we also searched references of relevant researches. No librarian assisted in the search process.

2.2. Eligibility criteria

Studies were eligible based on the following criteria: (1) Studies that directly compared between PCI and OMT in treatment of

patients with CTO and (2) studies which reported data on baseline characteristics and long-term clinical outcomes (details below). Redundant case reports, case series and ongoing studies were excluded after title and abstract review. By this process out of 108 articles 15 articles were selected for meta-analysis.^{4–6,12–23} Both observational and randomized studies were included. Articles published in languages other than English were not considered.²⁴ Abstracts accepted in conferences only were not included.²⁵ Studies which did not report outcomes of PCI and CABG were not included.²⁶

2.3. Data extraction

Two reviewers (DK and BJ) independently performed literature review, data extraction and data entry. Any disagreement between the reviewers was resolved by discussion until a consensus was reached. The extracted data included (1) details of the studies including title of the study, authors, publication year, study design, number of patients, duration of follow up; (2) baseline characteristics including age, gender, ejection fraction, presence of multi-vessel disease (MVD) or chronic kidney disease (CKD), left ventricular ejection fraction (LVEF); and (3) long term outcomes like major adverse cardiovascular events (MACE), mortality, myocardial infarction, stroke and un-planned revascularization.

2.4. Primary and secondary outcome

The primary outcome of the study was MACE which was comprised of cardiac death, myocardial infarction, stroke, un-planned revascularization. Secondary outcomes of the study were all-cause mortality, cardiac death, myocardial infarction, stroke and un-planned revascularization.

2.5. Quality assessment

The Newcastle–Ottawa Scale was used to appraise the quality of the studies. All studies with score of 5 and above were included in study.²⁷ ([Online supplemental material, supplement 4, quality of the studies](#)).

2.6. Data analysis and synthesis

Descriptive statistics are presented as means and standard deviations (SD) for continuous variables and number of cases or percentages for categorical variables. Statistical analysis was performed in line with PRISMA guidelines using Review Manager (RevMan version 5.3, the Cochrane Collaboration, London, United Kingdom, 2014).²⁸ Risk ratios (RRs) were used to pool differences in binary events, and mean differences (MD) with standard deviation (SD) were used to pool differences in continuous variables. The random effect model of DerSimonian and Laird was utilised as studies were heterogenous in design, diverse in outcome, and variable in follow up duration. Inverse variance methods were used to calculate effect sizes for continuous as well as dichotomous data.^{29,30}

Heterogeneity was assessed with the I^2 statistics. Funnel plots for the effects sizes of those variables were plotted where, a significant result is accompanied by high heterogeneity ($I^2 > 50\%$).³¹ Sensitivity analyses were conducted to those variables with high heterogeneity. Bi-variate analysis and meta-regression modelling was conducted using R, version 3.5.1 (package “metabin”) software to explain heterogeneity and bubble plot was constructed.³²

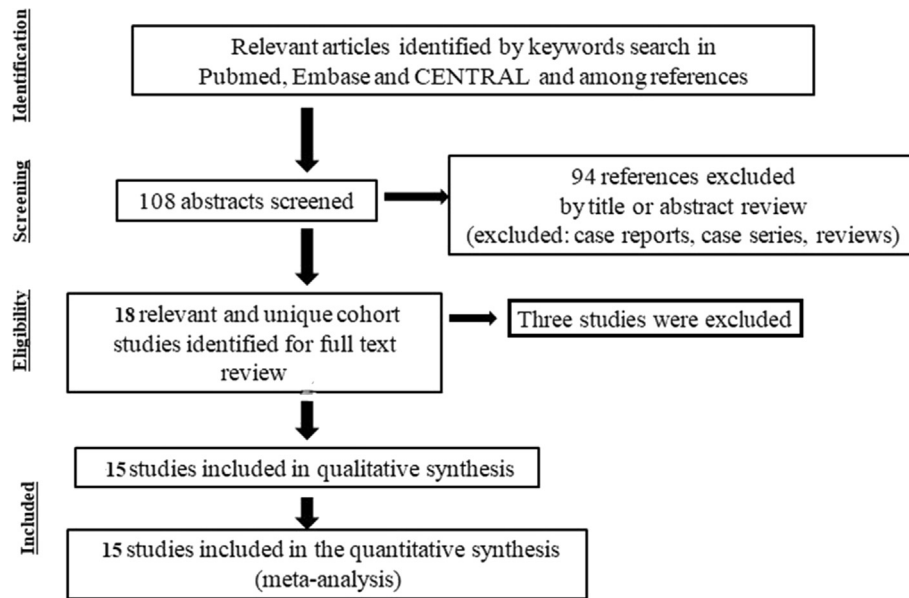


Fig. 1. Study selection process.

3. Results

In the meta-analysis of 15 studies, consisting of 6093 patients in the PCI group and 4943 patients in the OMT group, the median follow-up period was 5 years (1–8 years). Success rates in the PCI group ranged from 68% (in Arslan et al.,¹² 2006) to 99% (Mashayeki et al.,²³ in 2018) and overall complication rates ranged from 1 to 38% (Table 1).

3.1. Baseline characteristics

Baseline characteristics of the study cohorts have been depicted in Table 2. In the meta-analysis of the baseline characteristics, PCI+OMT group had lower mean age and lesser proportion of CKD and MVD but higher mean LVEF (Vide supplement 5, online supplemental material).

3.2. Primary outcome

Major adverse cardiovascular events (MACE) which comprises of cardiac death, myocardial infarction, stroke, and un-planned revascularization were significantly lower in the PCI+OMT group.

(RR: 0.76; 95% CI: 0.61 to 0.95; $P < 0.00001$; $I^2 = 84\%$) (Fig. 2A). High heterogeneity was partially (14%) explained by age factor. Higher age, TVD, CKD independently contribute to higher MACE in CTO patients undergoing PCI in multivariate logistic meta-regression analysis. However, follow-up duration and LVEF did not attribute significantly to heterogeneity, in isolation or in any combination in meta-regression model (Supplement 6, online supplemental material). Bubble plot of the variables were depicted in supplement 7, online supplemental material. In sub-group analysis, of MACE were not statistically different with respect to design of the study (whether randomized or not) ($P = 0.85$).

3.3. Secondary outcome

All-cause-mortality and cardiac deaths were significantly lower in the PCI+OMT group (Fig. 2B and C). Myocardial infarction and stroke rates were lower in the PCI+OMT group, however they did not reach statistical significance (Fig. 2D and E). Un-planned revascularizations (of any vessel) were similar among the PCI+OMT and the OMT only group (Fig. 2F).

Funnel plots of the primary and secondary outcomes were drawn which did not reveal any evidences of significant publication

Table 1
Procedural success and complications of percutaneous coronary intervention of chronic total occlusion.

Study	Success (%)	Complications (%)
Arslan 2006	117/172 (68%)	45/117 (38%)
Tomasello 2015	585/776 (75%)	28/776 (3%)
Ladwiniec 2015	250/405 (61%)	4/405 (1%)
Jang 2015	266/332 (80%)	26/332 (7%)
Hwang 2016	243/288 (84%)	35/288 (12%)
Yang 2016	699/883 (79%)	23/883 (2%)
Henriques 2016 (EXPLORE)	113/148 (77%)	40/147 (27%)
Choi 2017 (collateral)	319/373 (85%)	–
Werner 2018 (EuroCTO)	220/259 (85%)	11/254 (4%)
Ghou 2018	125/157 (80%)	–
Kim 2018 (CKD)	1020/1355 (75%)	–
Park 2018 (DECISION CTO)	417/459 (91%)	–
Rha 2018	439/479 (92%)	–
Choo 2018	424/448 (95%)	–
Mashayekhi2018 (REVASC)	100/101 (two attempts) (99%)	11/101 (11%)

Table 2
Base line characteristics of the meta-analysis cohorts.

Studies	Study design	Follow up (months)	Number of patients, n (successful PCI)		Age in years (Mean ± SD)		Male Gender n (%)		Left ventricular Ejection fraction (%) (Mean ± SD)		Presence of MVD n (%)		Presence of CKD n (%)	
			PCI	OMT	PCI	OMT	PCI ^b	OMT	PCI	OMT ^b	PCI	OMT ^b	PCI	OMT ^b
Arsilan 2006	Retrospective	50	117	115	61.1 ± 10.4	60.3 ± 10.6	88(75.2)	86(74.8)	50.0 ± 13.8	49.7 ± 14.5	78 (66.7)	80 (69.6)	—	6
Tomasello 2015 (IRCTO)	Prospective	12	776	826	67.0 ± 10.6	70.1 ± 12.5	658(84.8)	690(83.5)	52.1	40.8	481 (62)	545 (66)	56 (7.2)	107 (13)
Ladwiniec 2015	Retrospective	60	405	651	63.2 ± 10.1	65.8 ± 10.7	301(73.1)	506(77.7)	75.1	55.8	—	—	82 (20.3)	179 (27.5)
Jang 2015	Retrospective	60	332	236	61.6 ± 10.2	65.6 ± 12.0	419(83.5)	190(80.5)	56.9 ± 12.6	54.7 ± 13.0	390 (77.7)	186 (78.8)	40 (8.0)	29 (12.3)
Hwang 2016	Retrospective	96	288	147	59.7 ± 11.1	63.7 ± 11.1	231(80.2)	144(77.6)	58.6 ± 10.7	55.2 ± 12.9	—	—	20 (6.9)	14 (9.5)
Yang 2016	Prospective	96	883	664	61.5 ± 10.8	65.9 ± 11.3	713(80.7)	509(76.7)	57.6 ± 11.3	53.6 ± 12.9	595 (67.4)	517 (77.9)	68 (7.7)	61 (9.2)
Henriques 2016 (EXPLORE)	Randomized	4	148	154	60 ± 10	60 ± 10	131(89.0)	126(82.0)	41 ± 11	42 ± 12	62 (42)	67 (44)	—	—
Choi 2017	Prospective	60	305	335	62 ± 11	66 ± 11	230(75.4)	242(72.2)	53 ± 11	49 ± 12	22 (7.2)	61 (18.2)	19 (6.2)	23 (6.9)
Werner 2018 (EURO CTO)	Randomized	12	259	137	65.2 ± 9.7	64.7 ± 9.9	215(83.0)	118(86.1)	54.5 ± 10.8	55.7 ± 10.8	66 (25.5)	24 (17.5)	—	—
Chou 2018	Prospective	60	125	201	63.9 ± 9.7	64.8 ± 10.4	84(67.2)	157(78.1)	54.73 ± 7.4	51.7 ± 8.78	—	—	14 (11.2)	30 (14.9)
Kim 2018	Retrospective	60	1355	655	61.9 ± 11.0	65.9 ± 10.9	1106 (81.6)	503(76.8)	56.04 ± 17	53.5 ± 12.9	1039 (76.7)	508 (77.5)	185(13.6)	146(22.2)
Park 2018 (DECISION CTO)	Randomized	60	417	398	62.2 ± 10.2	62.9 ± 9.9	344(83.3)	319(81.6)	57.3 ± 9.8	57.6 ± 9.1	127 (30.8)	128 (32.7)	6 (1.5)	5 (1.3)
Rha 2018	Prospective	60	412	410	62.1 ± 10.8	66.1 ± 10.4	311(75.4)	290(70.7)	51.8 ± 11.1	48.3 ± 12.8	231 (56.0)	335 (81.7)	31 (7.5)	32 (7.8)
Choo 2018	Retrospective	12	424	474	61.3 ± 11.6	66.2 ± 11.1	308(72.6)	329(69.4)	56.0 ± 11.3	52.1 ± 12.6	140 (33.0)	257 (54.2)	28 (6.6)	50 (10.5)
Mashayeki 2018 (REVASC)	Randomized	12	101	104	65 (57–72) ^a	68 (61–74) ^a	91(90.1)	90(86.5)	54.7(42.9–65.1) ^a	59.6(45.8–64.3) ^a	53 (52.5)	61 (58.7)	—	—

NOS, New-Castle Ottawa Scale; OMT, Optimal Medical Therapy; PCI, Percutaneous coronary intervention; SD, standard deviation.

^a Expressed in median (maximum–minimum).

^b significantly higher in the respective meta-analysis cohort (Vide supplement 4, online supplemental material), MVD, Multi-vessel disease; CKD, Chronic Kidney Disease.

bias (supplement 8, online supplementary material, Funnel plot for publication bias). Sensitivity analyses were done and no particular study was found to be contributing decisively, as random effect model was undertaken. However, when three studies with maximum event rates (Ladwiniec et al.,¹⁶ Yang et al.,¹⁹ Kim et al.¹⁵) were excluded from the analysis, still the lower trend of MACE in the CTO PCI group was maintained [OR 0.80, 95% CI 0.60 to 1.07], though not statistically significant ($P = 0.13$).

4. Discussion

Major adverse cardiovascular events (MACE) rates were found to be significantly lower in the PCI+OMT group. In DECISION CTO study, PCI did not reduce the 4-year risk of MACE. However, nearly 20% of patients in the OMT group crossed over to PCI within 3 days after randomization, and that the study was stopped early due to slow enrolment.⁴ Moreover, more than 70% of patients had MVD and nearly half of patients in both groups received PCI for non-CTO lesions. In EURO-CTO study, MACE at 12 months was comparable with 6.7% in the OMT group and 5.2% in the PCI group.⁵ However, unlike DECISION CTO, in EUROCTO study all non-CTO lesions were treated before randomization. In the study by Jang, et al survival benefit was noted with CTO PCI in patients with well-developed collaterals also.¹⁵ In the study by Kim et al, PCI of CTO lesions among the non-CKD patients was associated with survival benefits.¹⁶ However, in patients with CKD, there were marginal differences between the PCI and OMT treatments in terms of long-term clinical outcomes. In the prospective non-randomized study by Yang et al., MACE was significantly lower in the PCI group in the real-world data but in the propensity matched analysis, the significance was lost.²⁰ However, rate of cardiac death was significantly lower in the CTO PCI group, especially with well-developed collateral flow as identified on subgroup analysis. Data obtained from UK Central Cardiac Audit Database revealed that successful CTO PCI was significantly associated with improved long-term survival independently from the treated CTO vessel ($P < 0.001$) and that the greatest improvement was obtained in case of complete revascularization ($P < 0.002$).³³ Unlike many other CTO PCI registries, Tomasello, et al. in IRCTO study, showed that PCI delivered a better cardiovascular outcome at 1-year clinical follow-up.¹⁹ Many of the studies were under-powered to determine the long-term outcome of CTO PCI and follow up duration was often inadequate. Moreover, there was slow enrolment and high cross over rates in randomized studies. So, when data of all the studies were pooled our meta-analysis showed a significant reduction of MACE in the PCI group. In this respect, the Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients with Chronic Total Occlusion trial (NCT01078051) is currently randomizing patients with CTO and stable angina to PCI vs. OMT to assess the impact of the intervention on cardiac mortality and MI during a follow-up of 5 years.

Understandably, age-group in the PCI group was lower as per the real world data. In the meta-regression model also, MACE was found to be significantly ($P = 0.03$) higher among aged patients who underwent PCI for CTO. PCI was less undertaken in the CKD patients as high contrast burden may worsen the peri-procedural outcome. In the study by Kim, et al., significant interaction (P for interaction = 0.014) was noted between kidney function and treatment strategy (revascularization vs. medical therapy) on all-cause death.¹⁶ In the meta-regression model also, MACE was found to be significantly ($P < 0.0001$) higher among CKD patients who underwent PCI for CTO. In patients with MVD, especially with high SYNTAX score PCI was less undertaken and often CABG was preferred. In the meta-regression model also, MACE was found to

4.1. Limitations

Limitations of this study are, firstly, the baseline cohorts were not similar. In the present meta-analysis, only four of the studies are randomised and all treated different cohorts of patients. DECISION CTO compared multi vessel PCI with or without CTO, REVASC did not determine myocardial viability while exploring role of CTO PCI on LV function, EXPLORE is in post STEMI patients only, randomised within 7 days after a STEMI, and EUROCTO is the only one addressing symptomatic benefit of PCI CTO in all comers.^{4–6,23}

Secondly, the long-term outcomes were not correlated to target vessel. However, studies have reported a survival benefit after successful versus failed CTO PCI in the left anterior descending (LAD) artery, but not in the right coronary artery (RCA) or the left circumflex (LCX) artery. Thirdly, the long-term outcomes were not correlated to PCI techniques (anterograde, subintimal re-entry or retrograde).³⁷ And last, most of the studies (except EXPLORE) did not report data on complete revascularizations and its impact on MACE and thus we cannot comment, whether complete revascularizations would have offered better outcome or not.³⁸

5. Conclusion

Despite the limitations, our meta-analysis emphasises the advantages of CTO PCI and goes along with the findings by Goa, et al., where they also found that successful CTO PCI using drug-eluting stents was associated with lower long-term mortality, lower risk of myocardial infarction, and lower risk of MACE.³⁹ The 2014 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization recommend CTO PCI to be considered in patients with expected ischemia reduction in a corresponding myocardial territory and/or angina relief (Class IIa, LOE B). They recommend an initial antero-grad approach and consideration of a retrograde approach if this fails or a primary retrograde approach in selected patients (Class IIb, LOE C).⁴⁰

In our meta-analysis consisting of 6093 patients in PCI group and 4943 patients in OMT group, it has been found that, PCI of CTO has a better long term outcome in terms of MACE, cardiac death and all causes of mortality with similar unplanned revascularization. Higher age, MVD, CKD independently contribute to higher MACE in CTO patients undergoing PCI in multivariate logistic meta-regression analysis. More number of randomized studies are necessary to evaluate the benefit in PCI in CTO patients in the real world scenario.

5.1. Impact on daily practice

Although the majority of interventional cardiologists in the past used to avoid CTO PCI attempts due to high radiation exposure and high probability of procedural failure and complications, the recent progress in equipment, techniques and accumulating clinical expertise has resulted in increased success rate, and the reduction of peri-procedural complications. This has encouraged the widespread usage of percutaneous approach in treating CTO lesions which resulted in favourable long-term outcomes including major adverse cardiovascular events, all-cause mortality as well as cardiac mortality with similar rates of unplanned revascularization.

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Declaration of competing interest

All authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2020.07.013>.

References

- Brilakis E. *Manual of Coronary Chronic Total Occlusion Interventions: A Step-by-Step Approach*. 2nd ed. Cambridge, MA: Elsevier; 2017.
- Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian multicenter chronic total occlusions registry. *J Am Coll Cardiol*. 2012;59(11):991–997.
- Ramunddal T, Høebers LP, Henriques JP, et al. Chronic total occlusions in Sweden- report from the Swedish coronary angiography and angioplasty registry (SCAAR). *PLoS One*. 2014;9:8.
- Lee SW, Lee PH, Ahn JM, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion: the DECISION – CTO trial. *Circulation*. 2019. <https://doi.org/10.1161/CIRCULATIONAHA.118.031313>.
- Werner GS, Martin-Yuste V, Hildick-Smith D, et al. EUROCTO trial investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. 2018;1–10, 0.
- Henriques JP, Høebers LP, Ramunddal T, et al. EXPLORE trial investigators. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE trial. *J Am Coll Cardiol*. Oct 2016;68:1622–1632.
- Høebers L, Claessen B, Elias J, Dangas GD, Mehran R, Henriques JP. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. *Int J Cardiol*. 2015;187:90–96.
- Iannaccone M, D'ascenzo F, Piazza F, et al. Optimal medical therapy vs. coronary revascularization for patients presenting with chronic total occlusion: a meta-analysis of randomized controlled trials and propensity score adjusted studies. *Cathet Cardiovasc Interv*. 2018;1–6.
- Ma Y, Li D, Li J, et al. Percutaneous coronary intervention versus optimal medical therapy for patients with chronic total occlusion: a meta-analysis and systematic review. *J Thorac Dis*. 2018;10:2960–2967.
- Zheng YY, Gao Y, Chen Y, et al. Outcomes of chronic total occlusions in coronary arteries according to three therapeutic strategies: a meta-analysis with 6985 patients from 8 published observational studies. *Braz J Cardiovasc Surg*. 2020 1;34:645–652.
- Khanra D, Duggal B, Basu Ray I, Kumar B, Walia R. 5193: Percutaneous coronary intervention provided better result than optimal medical therapy in patients with chronic total occlusion: a metanalysis. *Eur Heart J*. October 2019;40(suppl 1). <https://doi.org/10.1093/eurheartj/ehz746.0052>. ehz746.0052.
- Arslan U, Balcioglu AS, Timurkaynak T, Cengel A. The clinical outcomes of percutaneous coronary intervention in chronic total coronary occlusion. *Int Heart J*. 2006;47:811–819.
- Ghou L, Zhong L, Chen K, Wu J, Huang RC. Long-term clinical outcomes of optimal medical therapy vs. successful percutaneous coronary intervention for patients with coronary chronic total occlusions. *Hellenic J Cardiol*. 2018;59: 81–87.
- Hwang J, Yang JH, Choi SH, et al. Optimal medical therapy may be a better initial strategy in patients with chronic total occlusion of a single coronary artery. *Int J Cardiol*. 2016;210:56–62.
- Jang WJ, Yang JH, Choi SH, et al. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC (J Am Coll Cardiol)*. 2015;8:271–279.
- Kim CH, Yang JH, Park TK, et al. Revascularization vs. Medical therapy for coronary chronic total occlusions in patients with chronic kidney disease. *Circ J*. 2018;82:2136–2142.
- Ladwiniec A, Allgar V, Thackray S, Alamgir F, Hoyer A. Medical therapy, percutaneous coronary intervention and prognosis in patients with chronic total occlusions. *Heart*. 2015;101:1907–1914.
- Rha SW, Choi BG, Baek MJ, et al. Five-year outcomes of successful percutaneous coronary intervention with drug-eluting stents versus medical therapy for chronic total occlusions. *Yonsei Med J*. 2018;59:602–610.
- Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *Eur Heart J*. 2015;36:3189–3198.

20. Yang JH, Kim BS, Jang WJ, et al. Optimal medical therapy vs. Percutaneous coronary intervention for patients with coronary chronic total occlusion – a propensity-matched analysis. *Circ J*. 2016;80:211–217.
21. Choo EH, Koh YS, Seo SM, et al. Comparison of successful percutaneous coronary intervention versus optimal medical therapy in patients with coronary chronic total occlusion. *J Cardiol*. 2019;72:56–62.
22. Choi SY, Choi BG, Rha SW, et al. Percutaneous coronary intervention versus optimal medical therapy for chronic total coronary occlusion with well-developed collaterals. *J Am Heart Assoc*. 2017;6. e 006357. DOI: 10.1161/JAHA.117.006357.
23. Mashayekhi K, Neuser H, Kraus A, et al. Successful percutaneous coronary intervention improves cardiopulmonary exercise capacity in patients with chronic total occlusions. *J Am Coll Cardiol*. 2017;69:1095–1096.
24. Gai JJ, Gai LY, Zhai X, Zhang KY, Jin QH, Chen YD. Long-term outcome of patients undergoing recanalization procedures for chronic total coronary occlusion. *Nan Fang Yi Ke Da Xue Xue Bao*. 2015;35:1380–1383.
25. Wiggers H, Bøtker HE, Nielsen TT. Chronic total occlusions of coronary arteries—medical versus surgical treatment. *Scand Cardiovasc J*. 1997;31:297–303.
26. Fujino A, Sakamoto H, Fujino M, et al. No added benefits of percutaneous coronary intervention over medical treatment in patients with chronic total occlusions. *Eur Heart J*. 2013;34(suppl 1):P5319. <https://doi.org/10.1093/eurheartj/ehz310>. P5319.
27. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 12, 2016.
28. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials*. 1986;7:177–188.
30. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36:1–48.
31. Rucker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med*. 2008;27:746–763.
32. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22:2693–2710.
33. George S, Cockburn J, Clayton TC, et al. British cardiovascular intervention society; national institute for cardiovascular outcomes research. British cardiovascular intervention society; national institute for cardiovascular outcomes research. Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central car-diac Audit database. *J Am Coll Cardiol*. 2014;64:235–243.
34. Di Serafino L, Borgia F, Maeremans J, et al. The age, creatinine, and ejection fraction score to risk stratify patients who underwent percutaneous coronary intervention of coronary chronic total occlusion. *Am J Cardiol*. 2014;114:1158–1164.
35. Wijeyesundera HC, Norris C, Fefer P, et al. Relationship between initial treatment strategy and quality of life in patients with coronary chronic total occlusions. *EuroIntervention*. 2014;9:1165–1172.
36. Sapontis J, Salisbury AC, Yeh RW, et al. Early procedural and health status outcomes after chronic total occlusion angioplasty. A report from the OPEN-CTO registry (outcomes, patient health status, and efficiency in chronic total occlusion hybrid procedures). *JACC Cardiovasc Interv*. 2017;10:1523–1534.
37. Claessen BE, Dangas GD, Godino C, et al. Impact of target vessel on long-term survival after percutaneous coronary intervention for chronic total occlusions. *Cathet Cardiovasc Interv*. 2013;82:76–82.
38. Safley DM, House JA, Marso SP, Grantham JA, Rutherford BD. Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusions: variability by target vessel. *J Am Coll Cardiol Intv*. 2008;1:295–302.
39. Gao L, Wang Y, Liu Y, Cao F, Chen Y. Long-term clinical outcomes of successful revascularization with drug-eluting stents for chronic total occlusions: a systematic review and meta-analysis. *Cathet Cardiovasc Interv*. 2017;89:574–581.
40. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European society of cardiology (ESC) and the European association for cardiothoracic surgery (EACTS) developed with the special contribution of the European association of percutaneous cardiovascular interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619.