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Comparison of successful versus failed percutaneous coronary intervention in patients with chronic total occlusion: A systematic review and meta-analysis

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Abstract

Background: The optimal treatment strategy of chronic total occlusion (CTO) is currently debated. This meta-analysis aimed to evaluate the long-term clinical outcomes of successful percutaneous coronary intervention (PCI) of CTO.

Methods: Electronic databases were searched for studies comparing long-term outcomes between successful PCI in patients with CTO using drug-eluting stents and failed procedures. Meta-analysis was conducted with major adverse cardiac events (MACE) and all-cause mortality during the longest follow-up as endpoints. The combined hazard ratios (HRs) were applied to assess the correlation between successful CTO PCI and MACE/all-cause mortality.

Results: Eight studies consisting of 6,211 patients published between 2012 and 2020 met our inclusion criteria, and the CTO PCI success rate was 81.2%. Patients in the failed group were much older, and more likely to have morbidities (hypertension and

prior myocardial infarction), reduced left ventricular ejection fraction, and severe lesion characteristics (multivessel disease and moderate/severe calcification). Pooled results indicated that successful CTO PCI was significantly associated with prognosis. Compared to failed recanalization, patients receiving successful procedures had an improved MACE (HR: 0.50, 95% CI: 0.40–0.61, $p < 0.001$). Subgroup analyses further revealed the prognostic value of successful CTO PCI. However, no difference was observed regarding all-cause mortality (HR: 0.79, 95% CI: 0.61–1.02, $p = 0.074$). **Conclusions:** The present study showed that CTO recanalization was associated with improved long-term outcomes. However, randomized trials are needed to confirm the results due to the mismatch of baseline characteristics.

Key words: chronic total occlusion, percutaneous coronary intervention, major adverse cardiac events, meta-analysis

INTRODUCTION

According to the coronary Chronic Total Occlusion Academic Research Consortium (CTO-ARC) consensus recommendations, definite coronary chronic total occlusion (CTO) indicates CTO with typical appearance and definitive corroborating evidence of occlusion duration ≥ 3 months [1]. Typical appearance included Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow through the lesion with no thrombus, no staining at the proximal cap, and presence of mature collaterals. CTOs are highly prevalent among patients undergoing diagnostic coronary angiography, ranging from one-quarter to one-third of patients, though the prevalence is related to the group studied [2–6]. Patients with a history of coronary artery bypass graft (CABG) surgery are found to have CTOs of their native vessels more frequently (54%) [3], while patients presenting with ST-segment elevation myocardial infarction (STEMI) are less likely to have a CTO (10%) [7].

Chronic total occlusion was once treated as the last frontier of interventional cardiology for low success rates and potential for increased complications. In the past two decades, the rate of successful percutaneous coronary intervention (PCI) has steadily increased due to the development of equipment, progression of technology, and accumulation of operation experience. The 2011 ACCF/AHA/SCAI PCI guidelines recommend PCI of CTO in patients with appropriate clinical indications and suitable anatomy when performed by operators with appropriate expertise (Class IIa, level of evidence [LOE] B) [8]. As recommended by the ESC/EACTS guidelines on myocardial revascularization, percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel (Class IIa, LOE B) [9].

Although success rates for recanalization of CTO continue to improve, the optimal treatment strategy remains debatable. This meta-analysis was performed to compare long-term clinical outcomes of successful PCI using drug eluting stent (DES) versus failed PCI in patients with CTO.

The following article is presented in accordance with the PRISMA reporting checklist.

METHODS

Search strategy

A systematic search was conducted for eligible studies published in English in PubMed, MEDLINE, and Cochrane databases before July 2020. Search terms used include: “chronic total occlusion”, “coronary occlusion”, “percutaneous coronary intervention”, and “recanalization”. Additionally, the cited articles of the included studies and related reviews with the same topic were screened by the two authors of this study (M.Z. and M.D.Z.).

Inclusion criteria

Both prospective and retrospective studies were eligible for further evaluation. All of the CTO definitions were consistent with the CTO-ARC standard. For inclusion, studies needed to: focus on patients with single or multiple CTO with attempted PCI, have a patient population divided into successful and failed PCI groups, provide endpoint data of interest beyond one year, have adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the endpoints available, and use DES only. Studies that exclusively enrolled patients with acute myocardial infarction were excluded.

Additionally, unpublished data or conference abstracts were not considered for inclusion. All eligible studies for inclusion were reviewed to identify overlapping of the study population, and in these cases the most recent study with the largest sample size was used. Disagreements during article evaluation were resolved through discussion with another researcher (D.F.Z.).

Data extraction

The following information was collected from the included studies by two independent researchers (N.N. and Y.G.X.): the first author’s name, year of publication, study design, patient characteristics, intervention variables, and endpoints. For articles in which interested endpoints were not provided, emails were sent to the primary author for detailed information. A consultation regarding differences in data extraction was held with another researcher (D.F.Z.). Quality of the included studies was assessed using the Newcastle-Ottawa Scale. A study could be awarded a maximum of nine stars for quality, and studies with a score greater than seven were considered to be of high quality. Each study was assessed independently by two investigators (J.F.T. and C.Z.C.).

Endpoints

Most of the studies defined success CTO PCI as technical success, which was defined as achievement of TIMI grade 2 or greater antegrade flow in all ≥ 2.5 mm distal branches with < 30% residual stenosis of the target CTO lesion at the end of the procedure. Park et al. [14] defined as success of CTO revascularization procedure using DES implantation without serious procedure-related in-hospital deaths or major adverse events.

The following endpoints were collected from the eligible studies: the primary endpoint of major adverse cardiac events (MACE) and secondary endpoint of mortality from any cause during the longest follow-up. Follow-up periods were as reported in each study, which ranged from 1 year to 7 years. The definitions of MACE were also as those indicated in the individual studies. Most of the definitions, except the one carried by Park et al. [14] were the composite of death, myocardial infarction (MI), and target-vessel revascularization. Park et al. [14] defined MACE as all cause death or MI.

Statistical analysis

All statistical analyses were carried out using Stata 11.0 (Stata Corp, College Station, TX). The mean of continuous variables and percentage (%) of categorical variables were calculated. The associations between successful CTO PCI and endpoints were expressed as the HRs with their corresponding 95% CIs. Heterogeneity across studies were evaluated by Cochran's Q test and Higgins' I^2 statistic. The fixed effect model was adopted for nonsignificant heterogeneity (I^2 < 50%, $p > 0.1$). Publication bias was assessed by the visible plot and Begg's test. Sensitivity analysis was performed for the measurement of the reliability of the combined results.

Results

Search results

A literature search identified seven prospective trials and one retrospective trial published between 2012 and 2020 [10–17] which provided the HRs and 95% CIs in multivariate analysis for at least one of the endpoints, including 7 studies for MACE and 3 studies for all-cause mortality. If a study considered patients with failed CTO PCI as the reference, then the data was converted to HR estimations considering cases with successful CTO PCI as a reference group to reflect the impact of successful CTO PCI on CTO patients.

A total of 6,211 patients were included in these 8 studies. Figure 1 shows the inclusion and exclusion processes during the literature search process. Of these were 4 from Europe, 3 from Asia, and 1 from North America. Five were single-center experiences. The study characteristics and quality assessment results are shown in Table 1.

The final analysis comprised 5,044 patients who underwent successful recanalization of CTO lesions using DES and 1,167 patients with failed percutaneous interventions. The success rate of CTO PCI was 81.2%. **Supplementary Table** provides the demographic data, medical histories, and clinical characteristics of the included patients. In addition, summaries of variable means/percentages were calculated for the overall patient population. Compared with the successful recanalization patients, subjects in the failed group were much older (64.7 vs. 62.7 years, $p < 0.001$), more likely to suffer from hypertension (77.9% vs. 76.2%, $p = 0.004$), more likely to have a history of MI (37.5% vs. 29.9%, $p < 0.001$), have a left ventricular ejection fraction (LVEF) of ≤ 40% (15.8% vs. 11.9%, $p = 0.03$), have multivessel disease (MVD) (75.0% vs. 67.9%, $p < 0.001$), and have moderate-to-severe calcification (61.7% vs. 46.2%, $p < 0.001$). No differences were observed between successful and failed recanalization for male sex (82.8% vs. 84.2%, p =

0.13), current smokers (24.6% vs. 24.6%, p = 0.19), diabetes (33.7% vs. 33.1%, p = 0.60) or hypercholesterolemia (62.4% vs. 62.0%, p = 0.59).

Newcastle-Ottawa Scale quality assessment for the included studies indicated that all studies were of high quality. No publication bias for the included trials was observed.

Main outcomes

In summary, seven studies with a total of 4209 definite CTO patients reported the HRs for the association between successful recanalization of CTO lesions and MACE. Heterogeneity was not observed with an I^2 statistic of 41.7%, and the fixed effects model was selected. The pooled analysis showed that compared with failed CTO PCI, successful CTO PCI had a significantly lower MACE (HR: 0.50, 95% CI: 0.40–0.61, $p < 0.001$), which indicates that the successful recanalization of CTO lesions may decrease the risk of MACE (Fig. 2).

The prognostic values of successful CTO PCI were further displayed in subgroup analyses. The setting (single-center vs. multicenter) and follow-up time (≤ 3 years vs. > 3 years) did not affect the significant association between successful CTO PCI and improved MACE (Fig. 3).

Three studies with 3,552 subjects assessed the association between successful CTO PCI and all-cause mortality. No heterogeneity was observed across studies according to the I^2 statistic (0%) thus, the fixed effects model was selected. No significant difference was found in the combined results of long-term death of any cause (HR: 0.79, 95% CI: 0.61–1.02, p = 0.074) (Fig. 4).

Sensitivity analysis

Sensitivity analyses conducted by excluding one study at a time showed the results of the present analyses were relatively stable in this meta-analysis (Fig. 5).

Discussion

The present meta-analysis showed that patients receiving successful PCI for CTO lesions using DES suffered less from MACE than those who underwent failed procedures. However, no advantage was observed with regard to all-cause mortality. However, the results should be interpreted with a view of certain bias. Patients with failed intervention were much older, and more likely to have morbidities (hypertension and prior MI), reduced LVEF, and severe lesion characteristics (MVD and moderate/severe calcification), which have been shown to be poor prognostic factors in patients undergoing PCI. It is possible that the results represent the less favorable clinical profiles of patients with failed CTO PCI rather than the beneficial effects of successful CTO PCI. The worse outcome of the failed group might be partially due to a more severe coronary heart disease or to the insult produced by the attempt of intervention.

Chronic total occlusion implies total occlusion of coronary arteries and is related to worse prognosis in select patient populations. Van der Schaff et al. [18] reported mortality in STEMI patients with single-vessel disease, MVD, and a CTO of 8%, 16%, and 35%, respectively. CTO is an independent predictor of mortality in patients receiving primary PCI. Bataille et al. [19] also proved that CTO was independently associated with the occurrence of mortality in STEMI patients presenting with cardiogenic shock. Although it is thought that retrograde collateralization provides adequate blood flow to reduce ischemia, prior studies have shown that normal coronary flow reserve could only be achieved in less than 10% of CTO patients despite well-developed collateral circulation [20]. Sachdeva et al. [21] further reported that all patients with occluded coronary arteries showed an ischemic fractional flow reserve, even with severe regional dysfunction or well-developed collaterals.

Nowadays, PCI is becoming the preferred revascularization method due to the rapid advancement in equipment and techniques as well as a growing expertise among dedicated operators [22–27]. The rate of successful CTO PCI has increased to 90% in experienced institutions [28]. Several original studies and meta-analyses proved that successful PCI of CTO was related to decreased rates of adverse clinical outcomes, such as mortality, MI, and revascularization. However, CTO recanalization was associated with a much higher risk of complications in comparison with non-CTO interventions, especially perforation. Across multiple contemporary registries, tamponade occurred in 0.4% to 1.3% of cases. However, most of the evidence comes from observational research, which inevitably has a lot of potential bias.

To address the potential bias caused by the observational nature of studies comparing successful with failed PCI of CTO, recently, three randomized controlled studies compared CTO PCI versus optimal medical therapy in CTO patients; Decision-CTO [29], Euro-CTO [30], and REVASC [31]. Decision-CTO and Euro-CTO showed no advantage of CTO recanalization regarding the composite endpoint MACE, which was inconsistent with the REVASC trial. It is widely established that CTO PCI carries advantages in terms of improving symptoms compared with drug therapy alone except Decision-CTO. These differences could be due to the limitations found in the Decision-CTO trial, such as the slow and early termination of enrollment, the high percentage of cross-over in both arms, the high frequency of PCI for non-CTO lesions and the inclusion of patients with mild or absent symptoms. Meta-analysis including these randomized controlled trials (RCTs) and five observational studies revealed that CTO recanalization using DES was related to improved cardiac prognosis when compared with optimal medical therapy alone. However, no obvious difference was observed in the RCT subgroup consisting of 1,399 patients [32]. More RCTs are needed to explore the safety and efficacy of CTO PCI.

Current guidelines emphasize the critical role of evaluating viable myocardium in

patients presenting with coronary CTO [8, 9]. The major considerations when selecting individuals who are clinically appropriate and will gain improved prognosis from recanalization of occluded lesions are the presence or absence as well as the extent of myocardial viability. However, myocardial viability assessments are not currently standard processes in real-world clinical diagnosis and treatment.

Apparently, prior studies have been sub-optimally designed and performed. The absence of standardized end points and the discrepancy in definitions also prevent consistency and uniform interpretability of reported results in CTO intervention. CTO-ARC has provided uniform definitions for endpoints specific to CTO interventions and recommends a consensus framework for the design of clinical trials and registries.

Despite considerable retrospective and registry data suggesting a clinical benefit of PCI of a CTO, a clear demonstration of benefit from prospective randomized trials has not been forthcoming. Future trials using uniform definitions for endpoints may change the current landscape.

Limitations of the study

Since the study objective was to compare successful versus failed operations, the data of the current meta-analysis were obtained from observational trials without exception. The pooled results are affected by confounding factors, although the Newcastle-Ottawa Scale evaluation showed high quality. The baseline data and angiographic features of the two groups were obviously unbalanced, thus, the results could not be extended arbitrarily. In addition, post-discharge medication information was not collected in the original studies.

CONCLUSIONS

Despite certain limitations, this analysis showed that successful CTO PCI is

associated with improved long-term outcomes. However, the presented data are a comparison between successful and failed PCI of CTO, and any extrapolation of these results to compare PCI and medical treatment should be undertaken with caution. RCTs are needed to further optimize treatment strategies for CTO.

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Conflict of interest: None declared

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Table 1. Main characteristics of included studies.

Primary author, year published	Period	Region	Setting	Lesions	CTO definition	Procedural subgroups, n		Maximum follow-up	Completed follow-up	NOS
						Success	Failure			
Borgia, 2012	2003.04–2009.07	UK	Single-center	≥ 1 CTO	> 3 months, TIMI 0	237	65	4 years	100%	9
Niccoli, 2012	2005.06–2009.03	Italy	2 centers	1 CTO	> 3 months, TIMI 0	196	121	3 years	100%	9
Toma, 2016	2005.01–2013.12	Germany	Single-center	≥ 1 CTO	> 3 months, TIMI 0	1662	340	2.6 years	N/A	8
Lee, 2016	2003.03–2014.05	Korea	Single-center	≥ 1 CTO	≥ 3 months, TIMI 0	1004	169	4.6 years	100%	9
Park, 2016	2003.02–2006.03	Korea	2 centers	≥ 1 CTO	≥ 3 months, TIMI 0	253	124	7 years	100%	9
Wu, 2019	2016.08–2017.03	China	Single-center	≥ 1 CTO	≥ 3 months, TIMI 0	127	18	1 year	94.5	8
Xenogiannis, 2020	2012.01–2019.11	USA	multicenter	≥ 1 CTO	≥ 3 months, TIMI 0	1387	225	1 year	N/A	9
Stojkovic, 2018	2009.01–2010.12	Serbia	Single-center	N/A	≥ 3 months, TIMI 0	178	105	66 months	83.0%	9

CTO — chronic total occlusion; TIMI — Thrombolysis in Myocardial Infarction; N/A — not available; NOS — Newcastle-Ottawa Scale

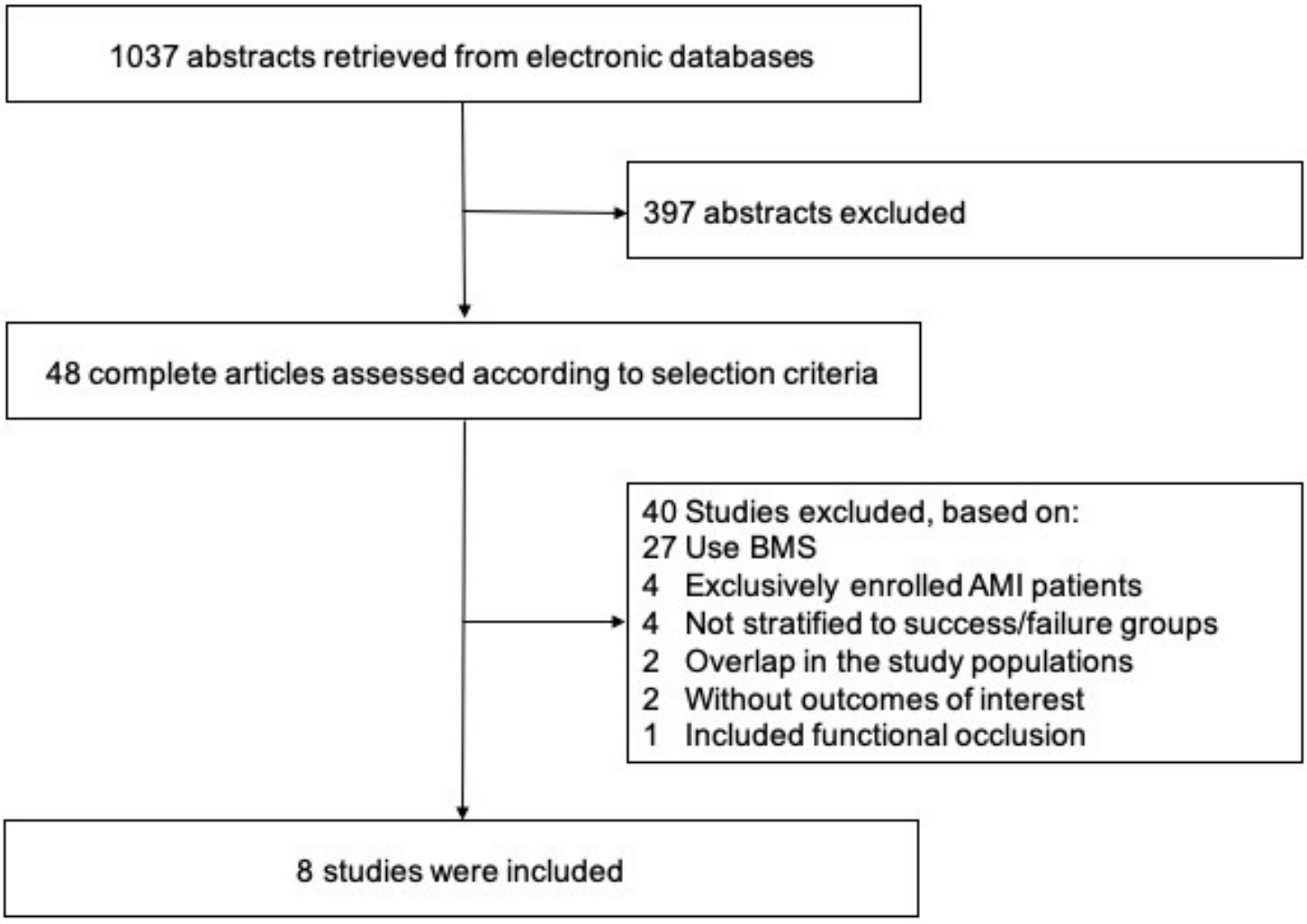
Figure 1. Flow diagram of study inclusion and exclusion criteria.

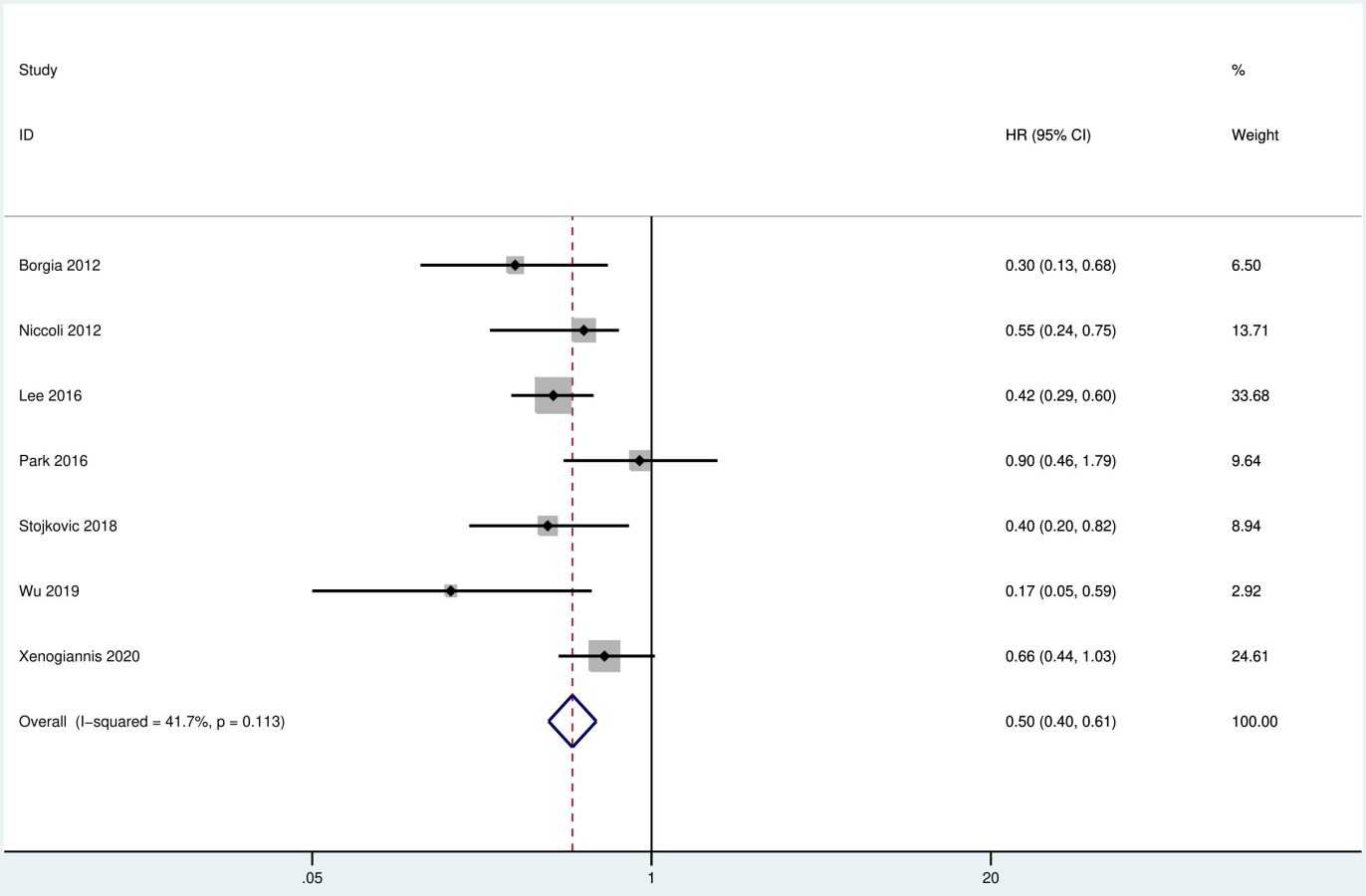
Figure 2. Forest plot for the correlation between successful chronic total occlusion percutaneous coronary intervention (CTO PCI) and major adverse cardiac events.

Figure 3. Forest plots for hazard ratios (HRs) of subgroup analyses for successful chronic total occlusion percutaneous coronary intervention (CTO PCI).

Figure 4. Forest plot for the correlation between successful chronic total occlusion percutaneous coronary intervention (CTO PCI) and all-cause mortality.

Figure 5. Sensitivity analysis for major adverse cardiac events.


1037 abstracts retrieved from electronic databases
397 abstracts excluded
48 complete articles assessed according to selection criteria
40 Studies excluded, based on:
27 Use BMS
4 Exclusively enrolled AMI patients
4 Not stratified to success/failure groups
2 Overlap in the study populations
2 Without outcomes of interest
1 Included functional occlusion
8 studies were included


Study
ID
HR (95% CI)
%
Weight
Borgia 2012
0.30 (0.13, 0.68)
6.50
Niccoli 2012
0.55 (0.24, 0.75)
13.71
Lee 2016
0.42 (0.29, 0.60)
33.68
Park 2016
0.90 (0.46, 1.79)
9.64
Stojkovic 2018
0.40 (0.20, 0.82)
8.94
Wu 2019
0.17 (0.05, 0.59)
2.92
Xenogiannis 2020
0.66 (0.44, 1.03)
24.61
Overall (I–squared = 41.7%, p = 0.113)
0.50 (0.40, 0.61)
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1
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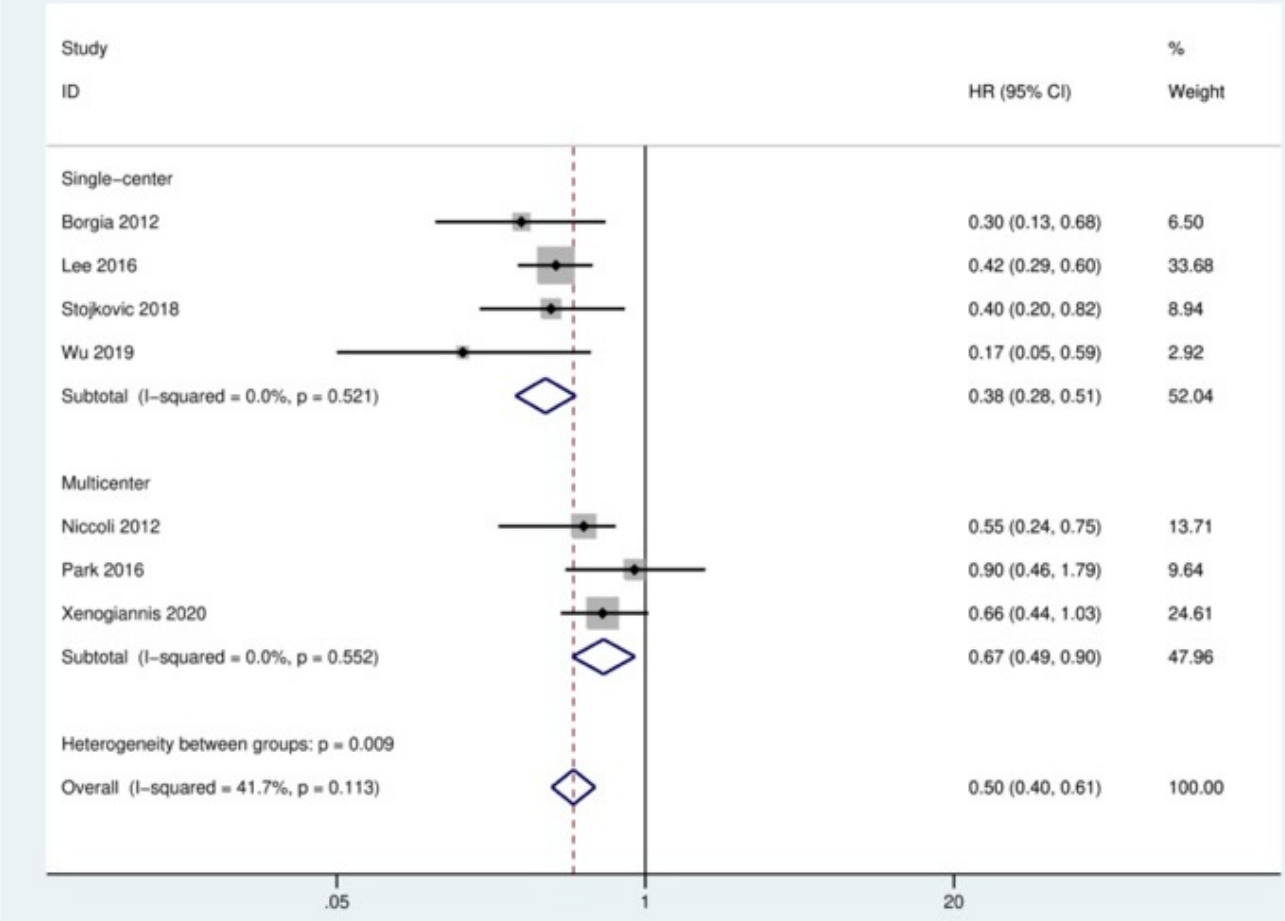
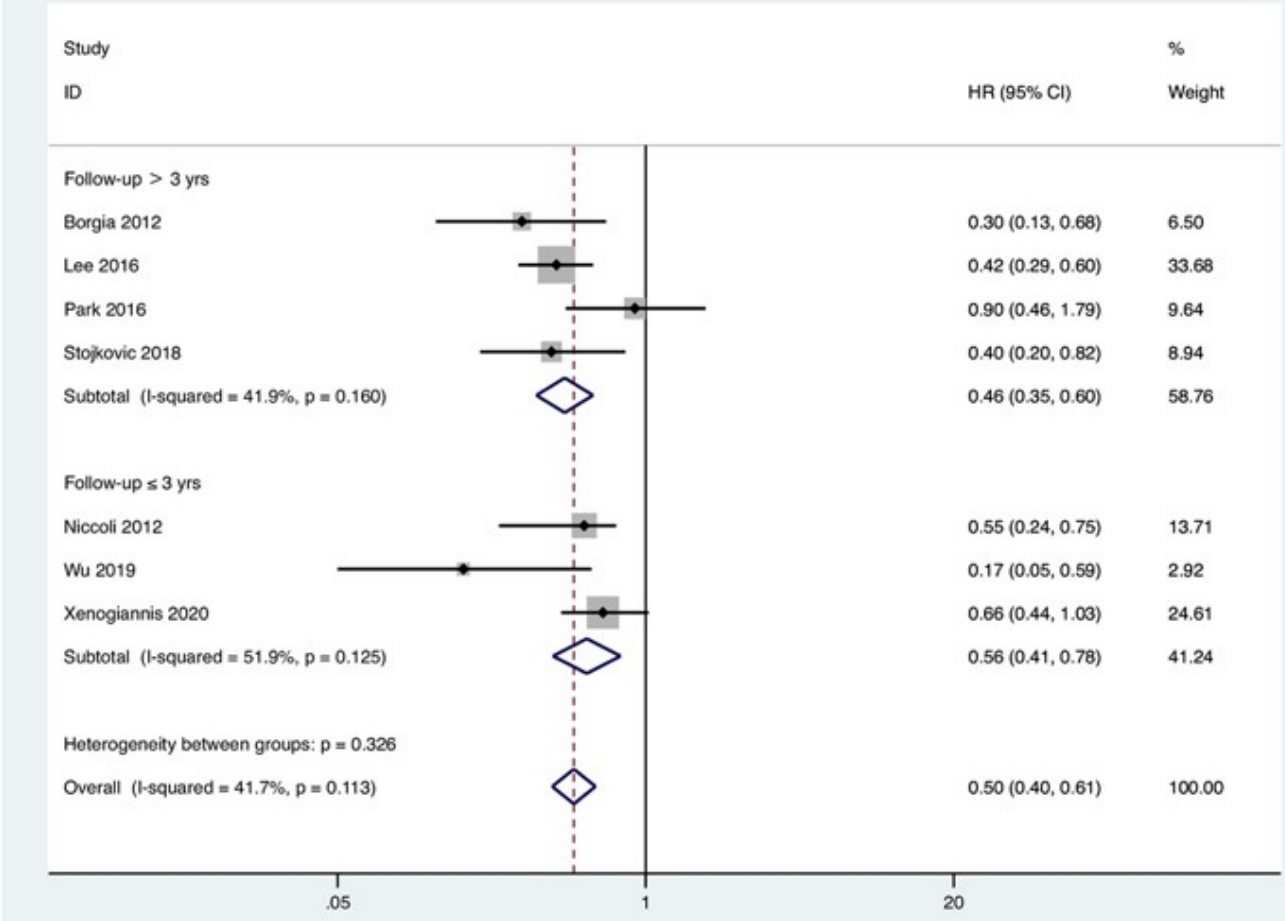
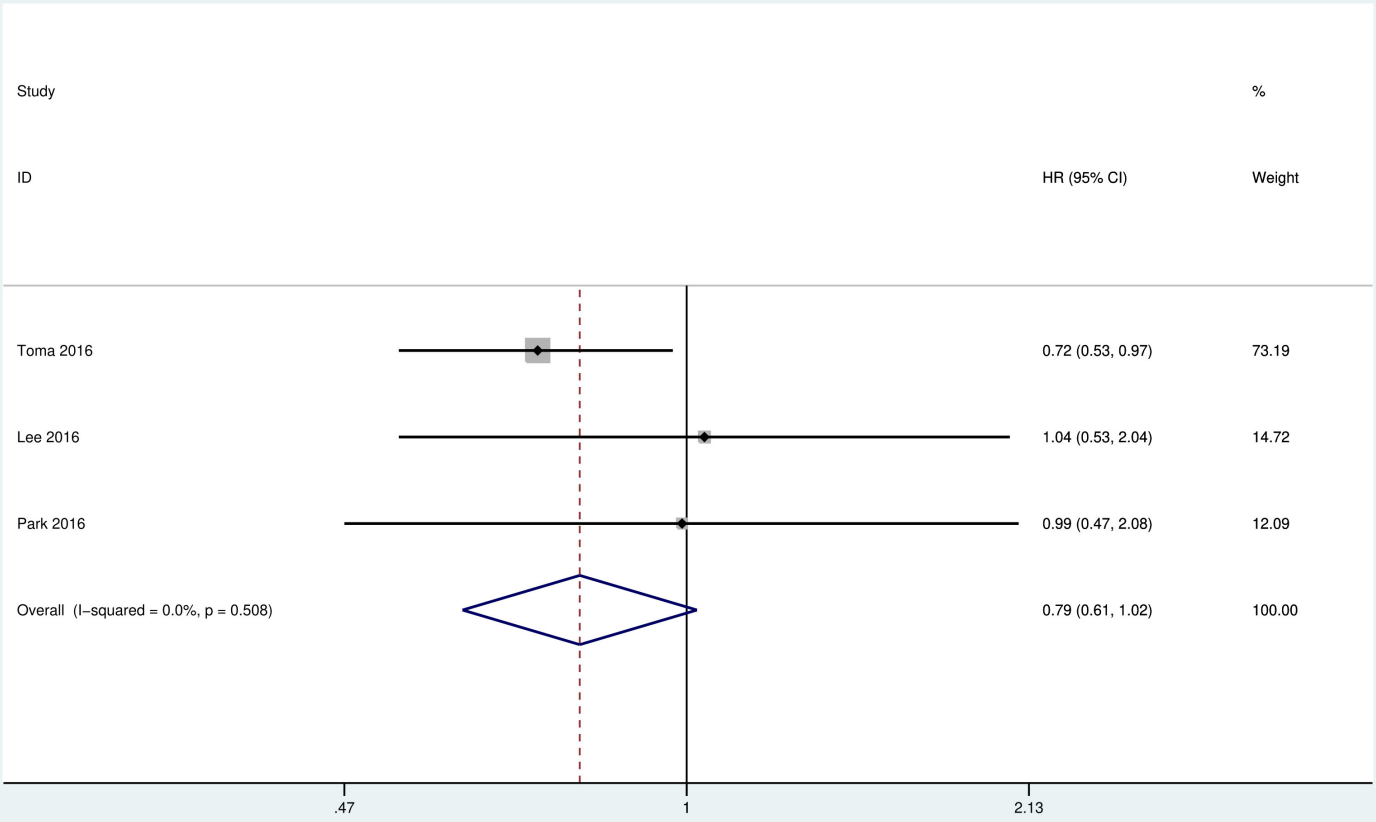
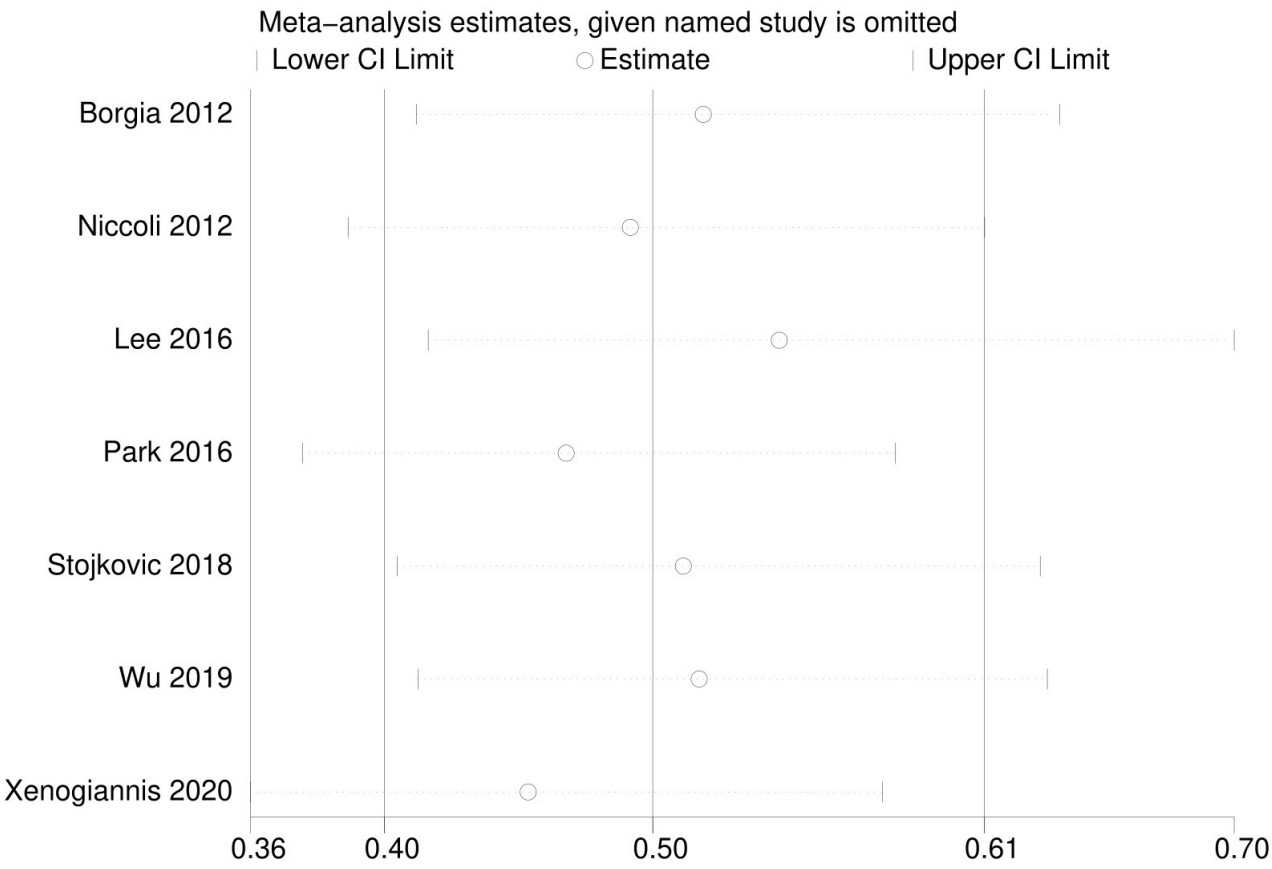

Study
ID
HR (95% CI)
%
Weight
Single−center
Borgia 2012
0.30 (0.13, 0.68)
6.50
Lee 2016
0.42 (0.29, 0.60)
33.68
Stojkovic 2018
0.40 (0.20, 0.82)
8.94
Wu 2019
0.17 (0.05, 0.59)
2.92
Subtotal (I−squared = 0.0%, p = 0.521)
0.38 (0.28, 0.51)
52.04
Multicenter
Niccoli 2012
0.55 (0.24, 0.75)
13.71
Park 2016
0.90 (0.46, 1.79)
9.64
Xenogiannis 2020
0.66 (0.44, 1.03)
24.61
Subtotal (I−squared = 0.0%, p = 0.552)
0.67 (0.49, 0.90)
47.96
Heterogeneity between groups: p = 0.009
Overall (I−squared = 41.7%, p = 0.113)
0.50 (0.40, 0.61)
100.00
.05
1
20


Study
ID
HR (95% CI)
%
Weight
Follow-up > 3 yrs
Borgia 2012
0.30 (0.13, 0.68)
6.50
Lee 2016
0.42 (0.29, 0.60)
33.68
Park 2016
0.90 (0.46, 1.79)
9.64
Stojkovic 2018
0.40 (0.20, 0.82)
8.94
Subtotal (I-squared = 41.9%, p = 0.160)
0.46 (0.35, 0.60)
58.76
Follow-up ≤ 3 yrs
Niccoli 2012
0.55 (0.24, 0.75)
13.71
Wu 2019
0.17 (0.05, 0.59)
2.92
Xenogiannis 2020
0.66 (0.44, 1.03)
24.61
Subtotal (I-squared = 51.9%, p = 0.125)
0.56 (0.41, 0.78)
41.24
Heterogeneity between groups: p = 0.326
Overall (I-squared = 41.7%, p = 0.113)
0.50 (0.40, 0.61)
100.00
.05
1
20


Study
ID
HR (95% CI)
%
Weight
Toma 2016
0.72 (0.53, 0.97)
73.19
Lee 2016
1.04 (0.53, 2.04)
14.72
Park 2016
0.99 (0.47, 2.08)
12.09
Overall (I–squared = 0.0%, p = 0.508)
0.79 (0.61, 1.02)
100.00
.47
1
2.13


Meta−analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Borgia 2012
Niccoli 2012
Lee 2016
Park 2016
Stojkovic 2018
Wu 2019
Xenogiannis 2020
0.36
0.40
0.50
0.61
0.70