Outcomes of Percutaneous Coronary Intervention Versus Optimal Medical Treatment for Chronic Total Occlusion: A Comprehensive Meta-analysis

Abdul A. Khan, MD, Muhammad F. Khalid, MD, Muhammad T. Ayub, MD, Ghulam Murtaza, MD, Rizwan Sardar, MD, Christopher J White, MD, Debabrata Mukherjee, MD, MS, Aravinda Nanjundappa, MD, and Timir K Paul, MD, PhD

Abstract: The presence of concurrent chronic total occlusion (CTO) is a strong predictor for both short-term and long-term mortality. Successful percutaneous coronary intervention (PCI) of CTO has been associated with clinical benefit. We sought to perform a meta-analysis comparing CTO-PCI versus optimal medical therapy. PubMed, ClinicalTrials.gov, Google scholar and the Cochrane Central Register of Controlled Trials were searched for studies published from 2006 to 2019. A total of 16 studies, with 11,314 patients were included. We analyzed data on mortality, cardiac deaths, myocardial re-infarction, major adverse cardiac events, stroke, and repeat CTO-PCI using random-effects models. The odds ratios (OR) with 95% confidence interval (CI) were computed and $P < 0.05$ was considered as a level of significance. Compared with medical therapy alone, CTO-PCI was associated with lower mortality (OR:

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0.45, CI: 0.32-0.63, $P < 0.00001$) and cardiac deaths (OR: 0.58, CI: 0.38-0.89, $P = 0.01$). These results were primarily driven by observational studies with no difference observed in randomized controlled trials. There was no significant difference in the incidence of major adverse cardiac events (OR: 0.71, CI: 0.48-1.05, $P = 0.54$), myocardial re-infarction (OR: 0.71, CI: 0.48-1.05, $P = 0.54$), stroke (OR: 0.61, CI: 0.32-1.17, $P = 0.14$, and repeat PCI (OR: 1.28, CI: 0.91-1.78, $P = 0.16$). This meta-analysis shows lower long-term mortality and cardiac deaths in CTO-PCI group as compared to OMT driven by observational studies with no difference observed in randomized controlled trials. Further randomized trials are needed to confirm these findings and evaluate long term results. (Curr Probl Cardiol 2021;46:100695.)

Introduction

In patients with coronary artery disease the presence of concurrent chronic total occlusion (CTO) is a strong predictor for both short-term and long-term mortality.[1-3] CTOs are prevalent in almost 20% of patients with coronary artery disease.[4] Despite recent advancements in procedural tools needed for intervention of coronary CTOs, treatment of these lesions comprises only 5% of the total percutaneous coronary intervention (PCI).[5] A major impediment to the wider adoption of CTO recanalization is the lack of robust clinical evidence. Prior observational studies have suggested beneficial effects of CTO recanalization in terms of symptoms, improved survival, reduced need for coronary artery bypass grafting (CABG) and a lower incidence of future myocardial infarction (MI).[6,7] However, these studies primarily involved nonrandomized comparisons of successful versus failed CTO-PCI. The recent addition of randomized controlled trials (RCT) to the pool of CTO literature has prompted a need to reconsider the optimal management strategy. The aim of this meta-analysis is to compare the outcomes of PCI versus optimal medical therapy (OMT) for CTO lesions with further evidence.

Methods

Data Sources

Electronic databases including MEDLINE, Cochrane CENTRAL (Central Register of Controlled Trials), Google Scholar and ClinicalTrials.gov were searched for all peer reviewed articles published until October 1, 2019 comparing outcomes for CTO lesions treated with OMT versus PCI. The following key words were used for the search; "chronic total occlusion," "CTO," "optimal medical therapy," "medical therapy," "PCI," "percutaneous coronary intervention," and "percutaneous transluminal coronary angioplasty," Articles not published in English language were excluded. Additionally, references of key articles identified by the electronic search were manually reviewed to find other potentially eligible articles. This meta-analysis is being reported in accordance with the PRISMA statement[8] and MOOSE Guidelines.[9]

Study Selection and End Points

Articles were selected if they satisfied the following inclusion criteria: (a) study included patients with chronic total occlusion, (b) study compared OMT with PCI, (c) study included at least 10 patients in each treatment group, (d) study reported at least one of the outcomes including long-term mortality, myocardial re-infarction, major adverse cardiac events, cardiac death, repeat revascularization, left ventricular ejection fraction and stroke.

To ensure inclusion of only peer reviewed data, we excluded review articles, and letters to the editor. The primary outcomes were major adverse cardiac events (MACE). The secondary end points were all cause mortality, myocardial re-infarction, cardiac death, repeat CTO revascularization, and stroke. MACE was defined as a composite of nonfatal stroke, nonfatal myocardial infarction (MI), and cardiovascular death.

Data Extraction and Quality Assessment

Two reviewers (MK, MA) independently screened all studies and assessed them for eligibility and quality of evidence. Prespecified data elements from all eligible studies were extracted into a standardized dataset including study characteristics, population under study, clinical outcomes and procedural characteristics. In case of disagreement, a consensus was reached using a third reviewer (AK).

The "Newcastle-Ottawa Scale" and Cochrane risk of bias tool were used for quality assessment of the included studies. The "Newcastle-Ottawa Scale" is recommended by the Cochrane Nonrandomized Studies Methods Working Group for assessment of observational studies.[10] The scale grades each study on 3 criteria; study group selection (maximum of 4 stars), comparability of the groups (maximum of 2 stars) and outcome assessment (maximum of 3 stars). Two independent reviewers (AK, MK) performed the Newcastle-Ottawa Scale grading. Discrepancies were resolved through mutual consensus.

Statistical Analysis

Mean difference (MD) or odds ratios (OR) were estimated with 95% confidence intervals (CI) for continuous variables and categorical outcomes respectively. Heterogeneity between studies was assessed using Cochran's Q statistic and the I^2 statistic.[11] A *P*value of ≤ 0.05 and I^2 value of 50% or more were considered as evidence of heterogeneity. Random effects model of DerSimonian and Laird was used to calculate pooled odds ratio (OR) and corresponding CI for the outcomes of interest. Publication bias was assessed by visual inspection of the funnel plot.[12] All analyses were performed using RevMan 5.3 statistical software. (The Cochrane Collaboration, Copenhagen, Denmark).[13]

Sensitivity analysis

Jackknife sensitivity analysis[14] was performed for each outcome of interest to verify the robustness of the results and the impact of each single study on the summary estimate of effect. Pooled estimates were recalculated using a random-effects model, each time with removal of a single study from the baseline group.

Results

Figure 1 depicts the study selection process. Sixteen studies[15-31] met the final selection criteria and were included in the analysis. The baseline characteristics of the included studies are presented in Table 1. Procedural characteristics are outlined in Table 2. Of the 16 studies, 7 were retrospective observational, 5 prospective observational, and 4 RCTs. The mean age of the participants was 62.9 ± 10.9 years in the CTO-PCI group and 66 ± 10.8 years in the CTO-OMT group. All the subjects were predominantly male. The definition of CTO, individual study procedural success rate and results are mentioned in Table 3. All studies were of

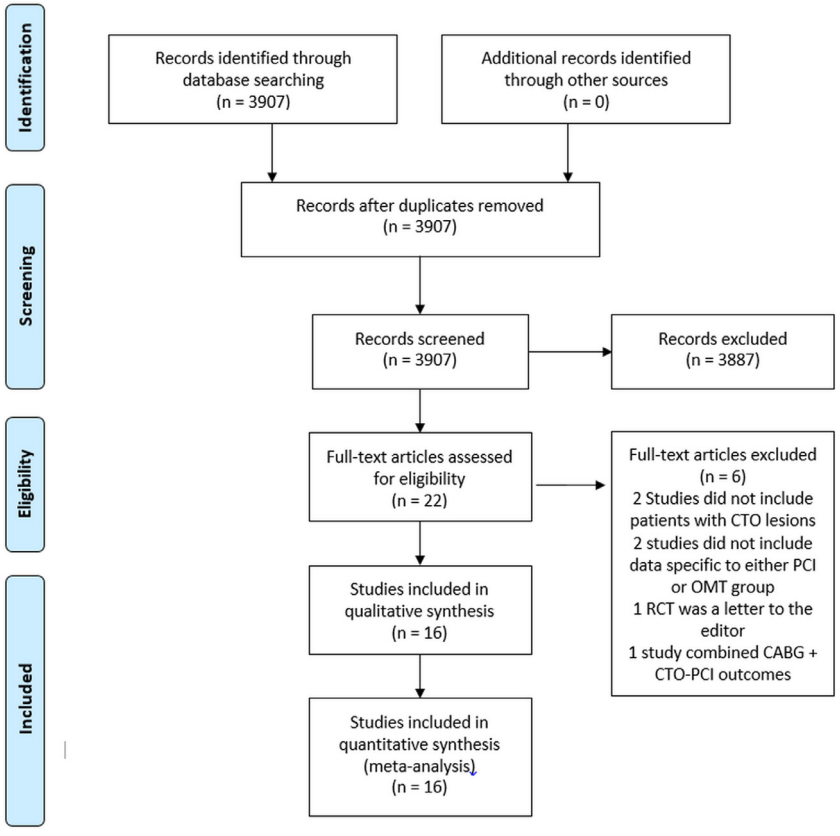

FIG 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) selection flow diagram.

sufficient quality to be included in the final analysis. Quality assessment of the studies by Newcastle-Ottawa scale is shown in Table 4. The details of the Cochrane risk of bias assessment for RCT are shown in Supplementary Figure 1.

A total of 11,314 patients with CTO treated either with PCI or OMT were included in this analysis. Of these, 5486 patients were in the CTO-PCI group and 5828 patients were in the OMT group. All the outcomes were heterogeneous except for stroke, as shown in Table 5. There was no evidence of publication bias for the primary outcome.

Primary Outcome

Primary and Secondary outcomes are shown in Figure 2. There was no statistically significant difference in overall MACE in the CTO-PCI

TABLE 1. Baseline characteristics of patients in included studies[15-31]

Variables	Arslan 2006 N = 232		Valenti 2014 N = 169		Park 2015/Lee 2019 (DECISION- CTO) N = 815		Jang 2015 N = 738		Tomasello 2015 (IRCTO) N = 1602		Lawdinec 2015 N = 1072	
	CTO-PCI	OMT/Failed CTO	CTO-PCI	Failed or nonattempted CTO-PCI	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	OMT
Number of patients	117	115	58	111	417	398	502	236	776	826	405	667
Age, years	61.1 ± 10.4	60.3 ± 10.6	64 ± 10	69 ± 14	62. ± 10.2	62.9 ± 9.9	61.6 ± 10.2	65.6 ± 12	67 ± 10.6	70.1 ± 12.5	63.2 ± 10.1	65.8 ± 10.7
Male sex %	75.2	74.8	85	73	83.2	81.4	83.5	80.5	84.8	83.5	73.1	77.7
Medical history %												
MI	40.2	45.2	19	29	10.9	8.8	–	–	41	45	49.9	60.5
PCI	–	–	–	–	15.1	19.1	16.5	28	32.3	30.9	5.4	9.8
DM	25.6	23.5	17	15	32.1	34.4	47.2	46.2	29.9	29.7	19.3	21
Smoke (Current)	35	38.3	50	30	30.4	26.4	30.5	21.7	41.8	46.5	18	24.5
PAD	–	–			–	–	–	–	10.1	17.6	9.4	15.8
HTN	40.2	42.6	55	67	63.5	60.7	63.7	65.7	77.8	78.1	55.6	53.6
Stroke	–	–	–	–	–	–	8	8.1	–	–	–	–
HLD	26.5	23.5	36	41	60.3	55.6	35.7	22.9	61.3	64.5	49.1	45
Family history of CAD	–	–			–	–	–	–	–	–	37.5	30.4
CKD >Stage 3	–	–	5.1	5.4	1.5	1.3	8	12.3	7.2	13	20.3	27.5
Chronic lung disease	–	–	–	–	–	–	–	–	8.9	11.7	5.7	7.8
Presentation												
Stable angina	–	–	8.6	13	72.3	74.9	–	–	45.9	32	91.6	75.4
UA/NSTEMI	–	–	–	–	20.4	19.4	20.7	14	19.8	22.4	7.9	13.2
STEMI	–	–	48	35	7.3	5.7	–	–	5.6	10.9	0.3	1.7
Arrhythmias	–	–	–	–	–	–	–	–	–	–	0.3	5.1

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TABLE 1. (*continued*)

Variables	Arslan 2006 N = 232		Valenti 2014 N = 169		Park 2015/Lee 2019 (DECISION- CTO) N = 815		Jang 2015 N = 738		Tomasello 2015 (IRCTO) N = 1602		Lawdinec 2015 N = 1072	
	CTO-PCI	OMT/Failed CTO	CTO-PCI	Failed or nonattempted CTO-PCI	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	OMT
Heart failure	–	–	–	–	–	–	–	–	–	–	0	4.6
LMS disease	–	–	19	9	–	–	0	0	–	–	0.3	3.5
Syntax score	–	–	–	–	21.2 ± 9.1	21 ± 9.5	23 ± 11	19.9 ± 10	–	–	10-19	9-21.5
Location of CTO												
LAD	29.9	29.6	32.8	17.1	44.5	41.6	40.6	21.7	–	–	–	–
LCx	41.9	38.3	32.8	27.9	10.2	10.9	33.9	33.1	–	–	–	–
RCA	28.2	32.2	34.5	55	45.3	47.5	46.8	51.7	–	–	–	–

Variables	Yang 2016 N = 1547		Hwang 2016 N = 435		Henriques 2016/Elias 2017 (EXPLORE) N = 302		Choi 2017 N = 640		Shuvy 2017 (CCN) N = 1115		Guo 2018 N = 326	
	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	No CTO-PCI	CTO-PCI	OMT/Failed CTO or residual CTO	CTO-PCI	OMT	CTO-PCI	OMT
Number of patients	883	664	288	147	148	154	305	335	266	849	125	201
Age, years	61.5 ± 10.8	65.9 ± 11.3	59.75 ± 11.1	63.73 ± 11.1	60 ± 10	60 ± 10	62 ± 11	66 ± 11	65.70 ± 10.18	65.82 ± 10.28	63.97 ± 9.71	64.84 ± 10.4

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TABLE 1. (*continued*)

Variables	Yang 2016 N = 1547		Hwang 2016 N = 435		Henriques 2016/Elias 2017 (EXPLORE) N = 302		Choi 2017 N = 640		Shuvy 2017 (CCN) N = 1115		Guo 2018 N = 326	
	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	No CTO-PCI	CTO-PCI	OMT/Failed CTO or residual CTO	CTO-PCI	OMT	CTO-PCI	OMT
Male sex %	80.7	76.7	80.2	77.6	89	82	72.2	75.4	80.7	72.7	67.2	78.1
Medical history %												
MI	20.4	31.8	22.9	38.1	13	16	20.3	19.7	30	19.2	27.2	29.9
PCI	20.2	31.3	23.6	36.7	6	10	–	–	–	–	6.4	10.4
DM	43.5	47.9	37.2	43.5	15	16	44.6	44.5	46.5	42.6	28	35.3
Smoke(Current)	32.3	27,4	32.6	28.6	52	49	37.7	37	30.2	30.3	–	–
PAD	2.6	6	2.8	3.4	–	–	7.9	11.9	9.1	6	4	4
HTN	61.9	66.1	52.4	61.9	40	45	64.3	67.8	88.9	86.5	68	70
Stroke	7.5	10.1	5.6	8.2	3	4	9.2	14	1.8	1.2	7.2	11.9
HLD	32.7	23.8	31.3	18.4	35	34	28.5	33.1	80.8	76	51.2	53.7
Family history of CAD	15.3	11	17.7	6.8	45	42	–	–	–	–	8.8	10.9
CKD >Stage 3	7.7	9.2	6.9	9.5	–	–	6.2	6.9	–	–	11.2	14.9
Chronic lung disease	–	–	–	–	–	–	–	–	7.7	6.9	8.8	6.5
Presentation												
Stable angina	–	–	106 ± 23	107 ± 26	–	–	–	–	–	–	–	–
UA/NSTEMI	24.3	14.8	94 ± 27	85 ± 21	–	–	12.8	12.2	–	–	–	–
STEMI	–	–			–	–	7.5	7.2	–	–	–	–

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TABLE 1. (*continued*)

Variables	Yang 2016 N = 1547		Hwang 2016 N = 435		Henriques 2016/Elias 2017 (EXPLORE) N = 302		Choi 2017 N = 640		Shuvy 2017 (CCN) N = 1115		Guo 2018 N = 326	
	CTO-PCI	OMT	CTO-PCI	OMT	CTO-PCI	No CTO-PCI	CTO-PCI	OMT/Failed CTO or residual CTO	CTO-PCI	OMT	CTO-PCI	OMT
			24 ± 9	32 ± 14								
Arrhythmias	–	–	–	–	–	–			–	–	–	–
Heart failure	–	–	–	–	–	–	11.5	17	–	–	16.8	27.9
LMS disease	–	–	–	–			4.9	9.9	10.1	10		
Syntax score	19.6 ± 8.8	19.8 ± 9.7	14.61 ± 6.6	11.9 ± 5.6	29 ± 8	29 ± 10	–	–	–	–	19.58 ± 7.18	23.31 ± 8.91
Location of CTO												
LAD	42.2	25.3	49.3	30.6	24	25	39	26.9	28.1	24.9	40.2	28.3
LCx	29.6	34.3	15.3	20.4	32	24	27.9	31.9	62.9	43.6	17.4	26.5
RCA	43.4	55.7	35.4	49	43	51	39.7	58.8	74.5	47	42.4	45.2

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TABLE 1. (*continued*)

Variables	Choo 2018 N = 898		Mashayekhi 2018 (REVASC) N = 205		Werner 2018 (EUROCTO) N = 396		Woon Rha 2018 N = 822	
	CTO-PCI	OMT	CTO-PCI +OMT	OMT+ Non CTO-PCI	CTO-PCI	OMT	CTO-PCI	CTO-OMT
Number of Patients	424	474	101	104	259	137	412	410
Age, years	61.3 ± 11.6	66.2 ± 11.1	65(57-72)	68(61-74)	65.2 ± 9.7	64.7 ± 9.9	62.1 ± 10.8	66.1 ± 10.4
Male sex %	72.6	69.4	90.1	86.5	83	86	75.4	70.7
Medical history %								
MI	13.7	19.4	38.6	36.5	22.8	18.3	–	–
PCI	–	–	27.7	31.7	56	51.8	–	–
DM	41.5	47.5	31.6	29.8	24.3	20.4	44.6	43.6
Smoke(Current)	23.1	23.9	22.8	20.2	73.4	67.2	38.1	35.8
PAD	–	–	22.8	25	–	–	8	12.1
HTN	62.5	59.3	80.2	89.4	73	71.5	62.8	67.5
Stroke	10.8	10.3	5	8.6	–	–	8.7	12.9
HLD	–	–	–	–	81.1	81	28.3	32.4
Family history of CAD	4.7	4.2	40.6	33.7	–	–	–	–
CKD >Stage 3/CKD	6.6	10.5	–	–	–	–	7.5	7.8
Chronic lung disease	–	–	–	–	–	–	–	–
Presentation %								
Stable angina	–	–	–	–	–	–	–	–
UA/NSTEMI	–	–	–	–	–	–	13.1	11.4
STEMI	–	–	–	–	–	–	8.7	9.2
Arrhythmias	–	–	–	–	–	–	–	–
Heart failure	–	–	–	–	–	–	11.6	17
LMS disease	4.2	6.8	–	–			–	–
Syntax score	–	–	14(9-22)	16(11-21)	–	–	–	–

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TABLE 1. (*continued*)

Variables	Choo 2018 N = 898		Mashayekhi 2018 (REVASC) N = 205		Werner 2018 (EUROCTO) N = 396		Woon Rha 2018 N = 822	
	CTO-PCI	OMT	CTO-PCI +OMT	OMT+ Non CTO-PCI	CTO-PCI	OMT	CTO-PCI	CTO-OMT
Location of CTO								
LAD	42.5	29.1	22.8	16.3	25.5	27	39.8	28.5
LCx	22.4	29.1	19.8	15.4	10.8	15.6	26.6	34.3
RCA	38.2	48.5	57.4	68.3	63.7	57.4	39.5	54.3

CAD, coronary artery disease; CCN, cardiac care network; CKD, chronic kidney disease; CTO, chronic total occlusion; CTO-PCI, chronic total occlusion-percutaneous coronary intervention; DECISOIN-CTO, drug-eluting stent implantation versus optimal medical treatment in patients with chronic total occlusion; DM, diabetes mellitus; EUROCTO, evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total occlusion; EXPLORE, evaluating Xience and left ventricular function in PCI on occlusions after STEMI; HLD, hyperlipidemia; HTN, hypertension; IRCTO, Italian registry of chronic total occlusions; LAD, left anterior descending artery; LCx, left circumflex artery; LMS, left main stem; MI, myocardial infarction; NSTEMI, non ST elevation myocardial infarction; OMT, optimal medical therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; REVASC, randomized trial to assess regional left ventricular function after stent implantation in chronic total occlusion; STEMI, ST elevation myocardial infarction; UA, unstable angina.

Table 2. Study design, methods, exclusion criteria and outcomes of included studies[15-31]

Study	Design	Patients (N)	Study period	Settings	Follow up	Exclusion criteria	Outcomes
Arslan 2006 N = 232	R	232	1999-2003	Single center	32 ± 12 months	Patient diagnosed with unstable angina, MI with or without ST segment elevation in preceding 3 months, prior CABG, or PCI	All-cause mortality: 1: Cardiac death related to STEMI, NSTEACS, Sudden cardiac death or congestive heart failure 2: Non cardiac deaths due to stroke or malignancy
Valenti 2014	R	169	2003-2012	Single center	3 years	In-hospital death during first week after primary PCI.	The primary endpoints were 1-year and 3-year cardiac survival.
Lawdinec 2015	P	1072	2002-2007	Single center	5 years	Previous CABG, moderate to severe mitral or aortic disease, active neoplasm	All-cause mortality, MI, MACE
Park 2015/Lee 2019 (DECISION- CTO)	RCT	815	2010-2016	Multicenter	3 years	LVEF<30%, Severe comorbidity	All-cause mortality, MACE, MI, Stroke, TVR
Jang 2015	R	568	2003-2012	Single center	42 months	Previous CABG, STEMI during preceding 48 hours, history of cardiogenic shock or cardiopulmonary resuscitation	MACE. Cardiac death, repeat revascularization, MI
Tomasello 2015 (IRCTO)	P	1602	2008-2009	Multicenter	1 year	Prior CABG and life expectancy <1 year	MACE, Stroke, Cardiac death, MI
Hwang 2016	R	435	2003-2012	Single center	47.6 months	Previous CABG, STEMI during preceding 48 hours, history of cardiogenic shock or cardiopulmonary resuscitation	MACE. Cardiac death, repeat revascularization, MI

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Table 2. (*continued*)

Study	Design	Patients (N)	Study period	Settings	Follow up	Exclusion criteria	Outcomes
Yang 2016	R	1547	2003-2012	Single center	45.8 months	Previous CABG, STEMI during preceding 48 hours, history of cardiogenic shock or cardiopulmonary resuscitation	Cardiac death, All-cause mortality, MI, MACE
Shuvy 2017 (CCN)	R	1115	2012-2013	Multi center	745 days	Prior CABG,ACS or MI within 3 months	Composite of mortality and hospitalization for MI
Henriques 2016/Elias 2017 (EXPLORE)	RCT	302	2007-2015	Multi center	3.9 years	Persistent or permanent atrial fibrillation, significant left main stenosis, CABG/ICD indication, severe valvular heart disease	MACE: Cardiac Death, MI, CABG, All-cause Mortality, LVEF, LVEDV, Stroke, Bleeding, Stent thrombosis
Choi 2017	P	640	2004-2015	Single center	5 years	Those who need CABG	All-cause mortality and hospitalization for MI, MACE, TVR, TLR, change in LVEF
Werner 2018 (EUROCTO)	RCT	396	2012-2015	Multicenter	12 Months	Patient not tolerating DAPT, elective non cardiac surgery within 6 months	Change in health status by SAQ, MACE, MI, Mortality
Guo 2018	R	326	2008-2010	Single center	47.2 $\pm$ 20 months	Previous CABG, STEMI during preceding 48 hours, history of cardiogenic shock or cardiopulmonary resuscitation, failed CTO-PCI, Malignant tumor	MACE, Cardiac death

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Table 2. (*continued*)

Study	Design	Patients (N)	Study period	Settings	Follow up	Exclusion criteria	Outcomes
Choo 2018	P	898	2004-2010	Multicenter	2.2 years	Prior CABG, failed CTO PCI	All- cause mortality, MACE, coronary revascularization either PCI or CABG, Recurrent MI
Mashayekhi 2018 (REVASC)	RCT	205	2017-2018	Single center	12 months	LVEF <25%, ACS within preceding 72 hours, Contraindications to cMRI	Primary endpoint was change in segmental wall thickening in the CTO territory, improvement in regional wall motion and changes in LVESV, LVEDV, LVEF, MACE
Woon Rha 2018	P	822	2004-2015	Single center	5 years	CTO in small vessel, or located side branch vessels, such as marginal, diagonal, septal and obtuse marginal artery	MACE: composite of total death, MI and revascularization either PCI or CABG.

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CCN, cardiac care network; cMRI, cardiac magnetic resonance imaging; CTO, chronic total occlusions; DAPT, dual antiplatelet therapy; DECISOIN-CTO, drug-eluting stent implantation versus optimal medical treatment in patients with chronic total occlusion; EUROCTO, evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total occlusion; EXPLORE, evaluating Xience and left ventricular function in PCI on occlusions after STEMI; IRCTO, Italian registry of chronic total occlusions; LVED, left ventricle end diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end systolic volume; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEACS, non ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; P, prospective; R, retrospective; RCT, randomized controlled trial; REVASC, randomized Trial to Assess Regional Left Ventricular Function after Stent Implantation in Chronic Total Occlusion; SAQ, Seattle angina questionnaire; STEMI, ST segment elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

Table 3. Definitions of CTO, procedure success rate and results of each study [15-31]

Study	CTO	Procedure success/Success Rate	Results
Arslan 2006	Defined as lesion exhibiting TIMI flow grade 0 of a native coronary artery.	PCI success rate was 68%.	There was no difference of rates of STEMI and stroke in between 2 groups. Heart failure was the major cause of death in both groups more in medical group 6.0% vs 4.8% ($P = 0.028$). Sudden cardiac death was the second most common of mortality.
Valenti 2014	Defined as a coronary obstruction with TIMI flow grade 0 and an established duration of >3 months.	CTO PCI success was defined as stenting of the target vessel with <30% residual stenosis and TIMI grade III flow to the distal vessel. Total success rate 78%.	The 1-year cardiac mortality rate was 1.7% in the successful CTO-PCI group and 12% in non attempted or failed CTO-PCI. Successful CTO-PCI was an independent predictor of 3-year cardiac survival.
Lawdinec 2015	Defined as complete coronary occlusion of ≥3 month's duration with thombolysis in myocardial infarction (TIMI) grade 0 flow.	CTO PCI success was defined as stenting of the target vessel with <30% residual stenosis and TIMI grade III flow to the distal vessel.	All-cause mortality at 5 years was 11.6% for CTO PCI and 16.7% for medical therapy HR 0.63 (0.40 to 1.00, $P = 0.052$). The composite of 5-year death or myocardial infarction occurred in 13.9% of the CTO PCI group and 19.6% in the medical therapy group, HR 0.64 (0.42 to 0.99, $P = 0.043$).
Park 2015/Lee 2019 (DECISION-CTO)	Defined as a coronary artery obstruction with TIMI flow grade 0 of at least 3 months duration based on patient history.	Overall CTO PCI success was 91%.	The primary endpoint MACE at 3 years in the intention-to-treat population of patients with a CTO was 20.6% in PCI group as compared to 19.6% in the optimal medical therapy group.
Jang 2015			

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Table 3. (*continued*)

Study	CTO	Procedure success/Success Rate	Results
	Defined as the obstruction of a native coronary artery with a TIMI flow grade 0 with an estimated duration longer than 3 months,	Defined as final residual stenosis $<20\%$ of the vessel diameter, with TIMI flow grade ≥ 2 after revascularization.	There was significantly lower incidence of cardiac death HR: 0.29; 95% CI: 0.15 to 0.58; $p < 0.01$) and MACE (HR: 0.32; 95% CI: 0.21 to 0.49; $p < 0.01$) in the revascularization group compared with the medication group.
Tomasello 2015 (IRCTO)	Defined as TIMI Grade 0 flow within the occluded segment with an occlusion duration >3 months.	Defined as a final residual stenosis, 30%, with a TIMI grade flow 3 after stent implantation.	At 1-year follow-up, patients undergoing PCI showed lower rate of major adverse cardiac and cerebrovascular events (MACCE) (2.6% vs. 8.2% and vs. 6.9%; P, 0.001 and P, 0.01) and cardiac death (1.4% vs. 4.7% and vs. 6.3%; P, 0.001 and P, 0.001) in comparison with those treated with Medical therapy.
Hwang 2016	Defined as obstruction of a native coronary artery with a TIMI flow grade of 0 and an estimated duration greater than 3 months.	Defined as a final residual stenosis less than 20% of the vessel diameter with a TIMI flow grade ≥ 2 after revascularization and without residual dissection assessed by visual estimation of angiograms.	There were no significant differences between the OMT group and PCI group with respect to MACE frequency (10.1% vs. 16.9%, adjusted hazard ratio [HR], 2.03; 95% confidence interval [CI], 0.88−4.68, $p = 0.10$) or cardiac death (OMT vs. PCI: 5.1% vs. 4.8%, HR, 1.14; 95% CI, 0.30−4.42, $p = 0.85$).

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Table 3. (*continued*)

Study	CTO	Procedure success/Success Rate	Results
Yang 2016	Defined as an obstruction of a native coronary artery with TIMI flow grade 0 for an estimated duration >3 months, based on the interval from the last episode of acute coronary syndrome or, in patients with no history of acute coronary syndrome, from the first episode of effort angina consistent with the location of the occlusion or previous coronary angiography.	Defined as final residual stenosis <20% and TIMI grade ≥2 flow after DES implantation, as assessed by visual estimation of the angiograms.	There was no significant difference in the rate of cardiac death between the OMT and PCI groups (hazard ratio, 1.57; 95% confidence interval, 0.91− 2.72, $P = 0.11$).
Shuvy 2017 (CCN)	Defined as coronary lesions with TIMI grade flow of 0 (true CTO) or TIMI grade flow 1 (functional CTO) and present for more than or equal to 3 months.	The overall success rate of CTO lesion in PCI group was 41.1%.	The rates of mortality or MI in patients with CTOs who were treated medically was 11.7%, which were significantly higher than in patients who were treated by CABG or by PCI (7.5% and 8.6%, respectively, p = 0.002).
Henriques 2016/ Elias 2017 (EXPLORE)	Defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels.	Defined as residual stenosis of the culprit lesion <30% and a Thrombolysis In Myocardial Infarction (TIMI) flow classification ≥2.	MACE was not significantly different between both arms (13.5% vs 12.3%, HR 1.03, 95% CI 0.54 to 1.98; $P = 0.93$). Cardiac death was more frequent in the CTO-PCI arm (6.0% vs 1.0%, $P = 0.02$) with no difference in all-cause mortality (12.9% vs 6.2%, HR 2.07, 95% CI 0.84 to 5.14; $P = 0.11$)

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Table 3. (*continued*)

Study	CTO	Procedure success/Success Rate	Results
Choi 2017	Defined as complete occlusion of the coronary main vessel with thrombolysis in myocardial infarction flow grade 0 for at least 3 month.	Defined as the achievement of an angiographic residual diameter stenosis of less than 30% with thrombolysis in myocardial infarction grade III flow.	CTO-PCI group had a lower hazard of myocardial infarction HR, 0.177; ($P = 0.039$; 95% CI, 0.03−0.91) and the composite of total death or myocardial infarction (HR, 0.298; $P = 0.017$; 95% CI, 0.11−0.80); however, it showed higher hazard of target lesion revascularization (HR, 3.942; $P = 0.003$; 95% CI, 1.58−9.81) and target vessel revascularization (HR, 4.218; $P = 0.001$; 95% CI, 1.85−9.60).
Werner 2018 (EUROCTO)	Defined as a complete occlusion (TIMI 0 flow) of at least 3 months duration, in a major coronary artery with a vessel diameter of at least 2.5 mm.	Defined as a final angiographic residual stenosis of <20% by visual estimate and TIMI III flow after implantation of biolimus-eluting stents,	There was a greater improvement of SAQ subscales was observed with PCI as compared with OMT for angina frequency [5.23, 95% CI 1.75-8.71; P = 0.003], and quality of life (6.62, 95% CI 1.78−11.46; P = 0.007).
Guo 2018	Defined as obstruction of a native coronary artery with a TIMI flow grade 0 of an estimated duration >3 months.	Defined as balloon dilation of the lesion <40% residual stenosis, or with stent placement <20% residual stenosis, with TIMI grade ≥2 flow after PCI according to visual estimation of the angiograms.	There was no significant difference between the 2 groups with respect to the prevalence of MACE (successful PCI vs. OMT: 29.6% vs. 21.9%, unadjusted HR 1.47, 95% [CI] 0.95-2.28, $P = 0.085$). After multivariate analyses, there were significant differences in the prevalence of MACE (adjusted HR 1.76, 95% CI 1.09-2.28, $P = 0.02$) and

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Table 3. (*continued*)

Study	CTO	Procedure success/Success Rate	Results
			repeated revascularization (2.14; 1.18-3.90, 0.01).
Choo 2018	Defined as coronary artery obstruction with TIMI flow grade 0 with estimated duration of the occlusion >3 months on the basis of history of chest pain or MI in the same target vessel, or the time made between coronary angiogram and PCI.	Defined as decrease in minimum stenosis diameter to <30% with TIMI flow grade ≥2 flow on coronary angiogram.	The primary end point of all-cause mortality was significantly reduced in CTO-PCI group as compared to medical group (10.6 vs 17.5% $P = 0.004$).
Mashayekhi 2018 (REVASC)	Defined as 100% stenosis and TIMI flow grade 0 of putatively >3 months duration, with estimate reference vessel diameter of 2.5-4.0 mm.	Defined as residual stenosis <30% with anterograde TIMI flow grade 3 in the CTO target vessel	There was no difference in SET between 2 groups CTO-PCI (4.1[14.6-19.3]) and no CTO-PCI (6.0[−8.6 to 6.0]). MACEs were significantly lower in CTO-PCI group (16.3% vs 5.9%, $P = 0.02$).
Woon Rha 2018	Complete obstruction of the coronary vessel by thrombolysis in myocardial infarction flow grade 0 for at least 3 months.	Overall CTO PCI success was 85%.	Successful CTO PCI with DESs was associated with a higher risk of repeat PCI for the target vessel, but lower incidence of death or MI.

CABG, Coronary artery bypass grafting; CCN, Cardiac care network; CI, Confidence interval; CTO, Chronic total occlusions**;** DECISOIN-CTO, Drug-eluting stent implantation versus optimal medical treatment in patients with chronic total occlusion; DESs, Drug eluting stents; DES, Drug-eluting stent; EUROCTO, Evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total occlusion; EXPLORE, Evaluating Xience and left ventricular function in PCI on occlusions after STEMI; HR, Hazard ratio; IRCTO, Italian registry of chronic total occlusions; MACE, Major adverse cardiac events; mm, Millimeter; OMT, Optimal medical therapy; PCI, Percutaneous coronary intervention; REVASC, Randomized Trial to Assess Regional Left Ventricular Function after Stent Implantation in Chronic Total Occlusion; SAQ, Seattle angina questionnaire; STEMI, ST segment elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction.

Table 4. Newcastle-Ottawa scale quality assessment[15-31]

Study	Study type	Selection	Comparability	Outcome/exposure
Arslan 2006	Observational	***	**	***
Valenti 2014	Observational	***	**	***
Lawdinec 2015	Observational	****	**	***
Park 2015/Lee 019 (DECISION- CTO)	RCT			
Jang 2015	Observational	***	**	***
Tomasello 2015 (IRCTO)	Observational	****	**	***
Hwang 2016	Observational	***	**	***
Yang 2016	Observational	***	**	***
Shuvy 2017 (CCN)	Observational	****	**	***
Henriques 2016/ Elias 2017 (EXPLORE)	RCT			
Choi 2017	Observational	****	**	***
Werner 2018 (EUROCTO)	RCT			
Guo 2018	Observational	***	**	***
Choo 2018	Observational	****	**	***
Mashayekhi 2018 (REVASC)	RCT			
Woon Rha 2018	Observational	****	**	***

CCN, cardiac care network; DECISOIN-CTO, drug-eluting stent implantation versus optimal medical treatment in patients with chronic total occlusion; EUROCTO, evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total occlusion; EXPLORE, evaluating Xience and left ventricular function in PCI on occlusions after STEMI; IRCTO, Italian registry of chronic total occlusions; RCT, randomized controlled trial; REVASC, randomized Trial to Assess Regional Left Ventricular Function after Stent Implantation in Chronic Total Occlusion.

group compared to the OMT group (OR: 0.82, CI: 0.62-1.08, $P = 0.16$). Subgroup analysis of RCTs and observational studies separately failed to show any significant differences.

Secondary Outcomes

All-cause mortality was significantly lower in the CTO-PCI group compared to the OMT group (OR: 0.45, CI: 0.32-0.63, $P < 0.00001$).

Table 5. Test of heterogeneity and publication bias for each outcome

Outcomes	Chi-square	df	*P* value	I Square (%)	Results	Publication bias
Mortality	23.92	10	<0.00001	58%	Heterogeneous	Yes
Myocardial re-infarction	33.99	14	0.10	59%	Heterogeneous	Yes
MACE	79.66	14	0.11	82%	Heterogeneous	No
Cardiac deaths	42.74	13	0.002	70%	Heterogeneous	Yes
Repeat-PCI	91.66	13	0.16	82%	Heterogeneous	Yes
Left ventricular function	11.2	3	0.01	73%	Heterogenous	No
Stroke	3.09	7	0.08	0%	Homogeneous	Yes

df, degrees of freedom; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

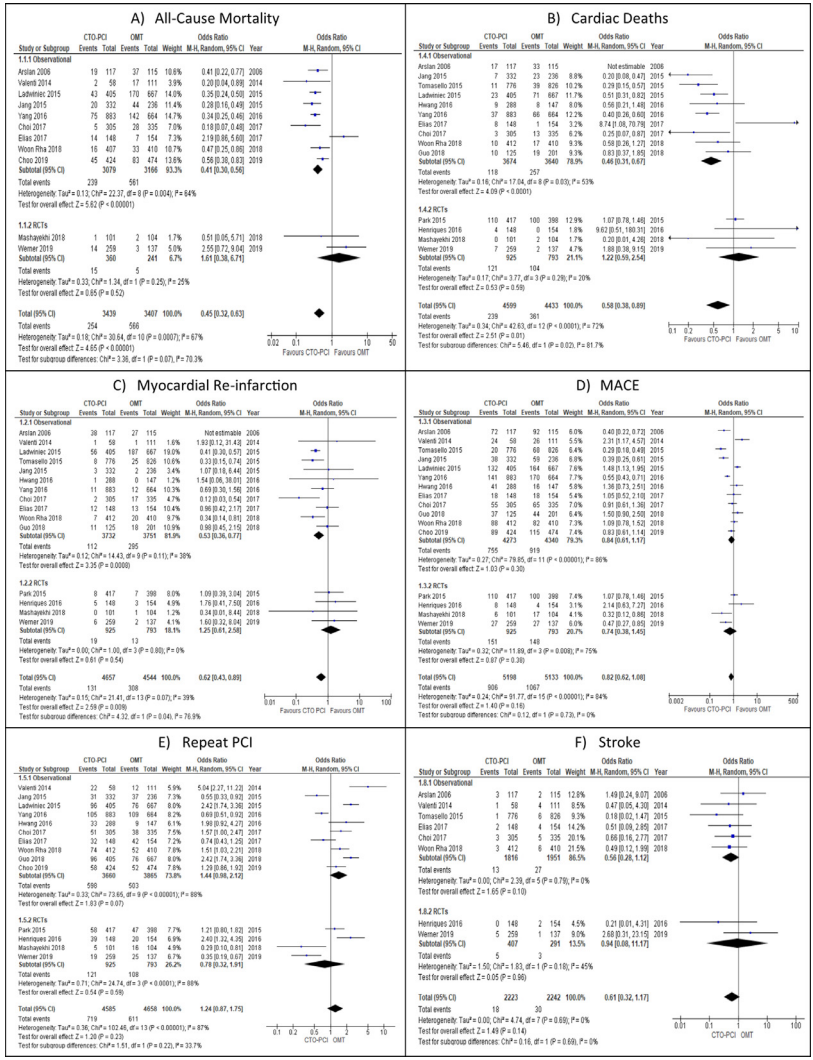

FIG 2. Forrest plots comparing CTO-PCI and OMT: (A) all-cause mortality, (B) cardiac deaths, (C) myocardial re-infarction, (D) major adverse cardiac events, (E) occurrence of repeat PCI, (F) stroke.

Similar trends were observed in terms of cardiac deaths (OR: 0.58, CI: 0.38-0.89, $P = 0.01$). These results were primarily driven by the observational studies, and subgroup analysis of RCTs alone revealed a nonsignificant improvement in these outcomes in favor of OMT. There was no statistically significant difference between 2 groups in other secondary outcomes including myocardial re-infarction (OR: 0.71, CI: 0.48-1.05,

$P = 0.54$), stroke (OR: 0.61, CI: 0.32-1.17, $P = 0.14$, CTO-re PCI (OR: 1.28, CI: 0.91-1.78, $P = 0.16$), and left ventricular ejection fraction (MD: 0.01, CI: −2.93, 2.96, $P = 0.99$—Fig 3).

Jackknife sensitivity analyses (Supplementary Table 2) excluding each study individually revealed no significant change in pooled ORs for all the outcomes except for myocardial re-infarction where exclusion of Arsalan et al. resulted in statistically significant results in favor of PCI group (OR: 0.62, CI: 0.43-0.89, $P = 0.01$). However, this study was graded to be high quality and therefore included in the final analysis. Separate subgroup analysis was performed including only RCTs.

Discussion

Studies have examined the relationship between the presence of CTO and mortality in various populations. The presence of CTO is associated with a higher mortality rate in patients with acute myocardial infarction, left main disease, or multivessel coronary artery disease (MVD).[1,3,32-34] The presence of CTO is also associated with a reduced left ventricular ejection fraction (LVEF <40%) and further deterioration of LVEF in ST segment elevation myocardial infarction (STEMI) patients. To date, compared with OMT, the impact of CTO-PCI are controversial and data on comparative assessment of successful CTO-PCI and OMT in patients with CTO are limited. Prior meta-analyses have revealed a survival advantage for patients with successful CTO revascularization compared to patients with failed CTO-PCI. However, this data was limited to observational studies and restricted in its clinical application to real world circumstances where CTO-PCI attempt rates remain below 15% on average,[9] and CTO PCI exhibits a considerably low procedural success rate (60%-86%), compared with PCI for non-CTO (98%).[14,19-21] In contrast, we investigated clinical outcomes of successful CTO-PCI versus OMT. We chose to include both observational studies and RCT in order to better understand the impact of CTO-PCI in all-comers.[18,24-26]

The optimal approach of dealing with CTO lesions has garnered intense interest in recent years. Recently, a meta-analysis including only 5 studies reported significantly reduced risk of all-cause mortality, cardiac death, and MACE in CTO-PCI patients compared to medical therapy. Lancone et al, revisited this topic with a total of 8 studies and found no significant differences in terms of overall MACE, re-PCI and MI. In contrast, our meta-analysis included 16 studies with almost 3 times the patient population along with recently published 3-year follow up data from the EURO-CTO PCI trial.

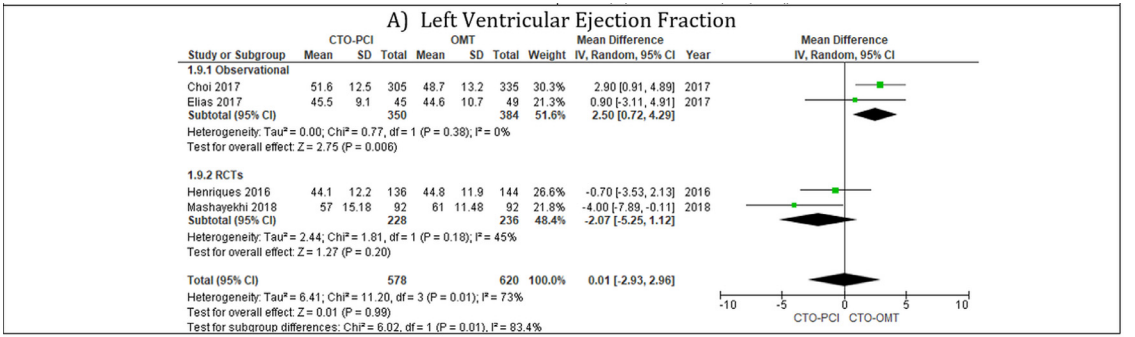

FIG 3. Forrest plot comparing left ventricular ejection fraction between CTO-PCI and OMT.

Our data reveals no significant differences in terms of overall MACE, myocardial re-infarction, stroke, revascularization, and LVEF between PCI and OMT. On the other hand, overall mortality and cardiac deaths were significantly lower in patients who underwent CTO-PCI. These results were primarily driven by observational studies and subgroup analysis including only RCT did not reveal any difference in these outcomes.

The survival benefit and reduced risk of MI offered by CTO-PCI in the present meta-analysis was offset by the higher rate of repeat-PCI when compared to OMT. Several possible explanations for these results can be postulated. Vascular remodeling and vasospasm associated with CTO PCI can make the appropriate choice of stent size quite challenging leading to suboptimal stent deployment unless imaging modality is used.[35] Higher burden of atherosclerosis, and dense calcification may hinder sufficient stent expansion.[36] Furthermore, CTO lesions often have an unfavorable response to DES when evaluated by optical coherence tomography, indicating the important pathological link between lesion morphology underneath the stents and heterogeneous artery healing.[37]

Patients with STEMI, and nonrevascularized CTO lesions often present with higher rates of cardiogenic shock at admission.[38-40] Such patients often have higher comorbidity burden, poorer myocardial reserve, and lack of collaterals to the infarct-related artery.[2,40,41] A recent meta-analysis involving more than 14,000 patients with STEMI showed approximately 3-fold increase in long-term all-cause mortality in patients with a CTO in noninfarct related artery comparing without a CTO. Although exact mechanisms underlying decreased mortality associated with PCI to CTO lesions remains elusive, it has been speculated that improved contractile function of hibernating myocardium, recovered LVEF, and improved electrical stability resulting from myocardial salvage may be responsible. Similarly, CTO lesions, especially infarct-related, are associated with high risk of life threatening arrhythmias and sudden cardiac death.[42,43]

Our study revealed no differences in terms of LVEF between CTO-PCI and OMT in contrast to a prior meta-analysis showing improved LVEF.[44] It is important to note that most of the studies included in our analysis did not assess this outcome in particular and our analysis is therefore underpowered for this particular outcome.

This study reveals difference in the outcomes between observational data and RCTs regarding long-term mortality and cardiac deaths. There are a number of possible explanations for this inconsistency. First, all the RCTs (Euro CTO, REVASC trials, EXPLORE, DECISION-CTO),[18,24-26] included in this analysis were underpowered due to slow enrollment rates

and had a high crossover rate introducing significant selection bias. The DECISION-CTO trial in particular experienced cross over rates as high as 20%. Second, majority of these trials involved enrollment of a minimally symptomatic population with relatively lower angina scores, and a better comorbidity index. One could argue that the patients who would benefit the most from such procedures were excluded during enrollment leading to no change in hard outcomes as observed in this analysis. Nonetheless, 2 recent studies point to increased risk of complications with CTO-PCI that are consistent with the results of RCTs. A study by Hirai et al. showed a perforation rate of 8.9% in 1000 consecutive patients, nearly half of these were clinically significant events resulting in in-hospital mortality of approximately 10%.[45] A recent article by Goliasch et al. also describes a significantly increased mortality in patients who have Troponin elevation during CTO interventions.[46]

This meta-analysis has several limitations. This study lacks individual level data and includes data from both RCTs and observational studies. Due to lack of available data, we were unable to perform subgroup analysis comparing the effects of different coronary distributions and LV function on the overall hard outcomes. Heterogeneity exists between different studies; however the study effect was limited as shown by the Jackknife sensitivity analysis. We used random effects model to alleviate the effect of heterogeneity. There were few differences in the inclusion criteria of all the studies in this analysis. As such this meta-analysis should be viewed as hypothesis generating until further evidence is available. None of the studies mentioned use of invasive imaging techniques such as IVUS or OCT to optimize stent delivery in the CTO-PCI arm as part of their routine protocol. Some observational studies also included patients with failed CTO-PCI in the OMT arm which may bias the results in favor of CTO-PCI. Observational studies typically enrolled only successful PCI cases in the CTO-PCI arm, whereas RCTs included up to 20%-30% of failed PCI in the CTO-PCI arm as well, thus adding potential bias to the overall result.

Conclusion

This meta-analysis shows lower long-term mortality and cardiac deaths in CTO-PCI group as compared to OMT driven by observational studies without any difference seen in RCTs. Further randomized trials are needed to confirm these findings and evaluate long term results.

Authors' contribution

Abdul Ahad Khan: Conceptualization, Software, Methodology, Formal Analysis, Data Curation, Validation, Writing – Original Draft preparation, Review & Editing. ***Muhammad F. Khalid:*** Data Curation, Writing – Review & Editing. ***Ghulam Murtaza:*** Data Curation, Writing – Review & Editing. ***Muhammad Ayub:*** Writing – Review & Editing. ***Rizwan Sardar:*** Writing – Review & Editing. ***Christopher J White:*** Writing – Review & Editing. ***Debabrata Mukherjee:*** Writing – Review & Editing. ***Aravinda Nanjundappa:*** Writing – Review & Editing. ***Timir K Paul:*** Writing – Review & Editing, Supervision.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2020.100695.

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