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CHRONIC TOTAL OCCLUSION

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Meta-analysis of the impact of successful chronic total occlusion percutaneous coronary intervention on left ventricular systolic function and reverse remodeling

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Background: We sought to examine the impact of coronary chronic total occlusion (CTO) percutaneous coronary intervention (PCI) on left ventricular (LV) function.
Methods: We performed a systematic review and meta-analysis of studies published between January 1980 and November 2017 on the impact of successful CTO PCI on LV function.
Results: A total of 34 observational studies including 2735 patients were included in the meta-analysis. Over a weighted mean follow-up of 7.9 months, successful CTO PCI was associated with an increase in LV ejection fraction by 3.8% (95%CI 3.0-4.7, $P < 0.0001$, $I^2 = 45\%$). In secondary analysis of 15 studies (1248 patients) that defined CTOs as occlusions of at least 3-month duration and reported follow-up of at least 3-months after the procedure, successful CTO PCI was associated with improvement in LV ejection fraction by 4.3% (95%CI [3.1, 5.6], $P < 0.0001$). In the 10 studies (502 patients) that reported LV end-systolic volume, successful CTO PCI was associated with a decrease in LV end-systolic volume by 4 mL, (95%CI −6.0 to −2.1, $P < 0.0001$, $I^2 = 0\%$). LV end-diastolic volume was reported in 9 studies with 403 patients and did not significantly change after successful CTO PCI (−2.3 mL, 95%CI −5.7 to 1.2 mL, $P = 0.19$, $I^2 = 0\%$).
Conclusions: Successful CTO PCI is associated with a statistically significant improvement in LV ejection fraction and decrease in LV end-systolic volume, that may reflect a beneficial effect of CTO recanalization on LV remodeling. The clinical implications of these findings warrant further investigation.

KEYWORDS
chronic total occlusion, ejection fraction, left ventricular function, left ventricular reverse remodeling

1 | INTRODUCTION

Coronary chronic total occlusions (CTOs) are common and have been associated with increased risk for ventricular arrhythmias and adverse clinical outcomes.[1–4] Several studies, most of which were retrospective, have examined whether CTO revascularization improves symptoms, and most have suggested a benefit.[5,6]

The effect of successful CTO revascularization on left ventricular (LV) systolic function remains unclear, with the only randomized controlled trial performed to date demonstrating no benefit from CTO recanalization in the setting of recent ST-segment elevation acute myocardial infarction.[7] We performed a systematic review and meta-analysis to examine the impact of successful CTO PCI on LV size and ejection fraction (EF).

2 | METHODS

2.1 | Data sources and eligibility criteria

Our meta-analysis was conducted and reported according to the proposal for conducting and reporting Meta-analyses of Observational studies (MOOSE)[8] and was registered with the International Prospective Register for Systematic Reviews (PROSPERO: CRD42018084926). We performed a computerized systematic search through MEDLINE, EMBASE, and COCHRANE databases from January 1980 to November 2017 using the following search terms separately and in combination; "CTO," "Chronic total occlusion," "Chronic total coronary occlusion," "revascularization," "PCI," "Angioplasty," and "Recanalization." A similar search strategy was performed for abstracts of the major scientific sessions (American College of Cardiology, European Society of Cardiology, American Heart Association) until November 2017. We further screened the bibliographies of the retrieved studies, prior meta-analyses as well as ClinicalTrials.gov for any relevant studies not retrieved through the initial search. Our search was limited to the English language.

We included in this meta-analysis studies that evaluated the impact of successful CTO PCI on LVEF. Studies had to include patients with a CTO (definition of CTO in each study is illustrated in Table 1) who received successful PCI, and the LV function had to have been assessed before and after successful PCI.

2.2 | Data extraction and quality assessment

The data were extracted by two independent investigators (MM, MS) including baseline study characteristics, patients' demographic and outcomes of interest from the retrieved studies. Discrepancies among investigators were settled by consensus. The quality of the included studies was assessed using New-Castle Ottawa Scale for cohort studies.[9]

2.3 | Outcomes

The primary outcome of the current study was the mean difference in LVEF before and after successful CTO PCI. Secondary outcomes included the mean difference in left ventricular end-diastolic volume (LVEDV) and Left ventricular end-systolic volume (LVESV) before and after successful PCI. To ensure homogeneity in the outcome definitions, we included the reported volumes (mL) rather than volume indices (mL/m^2) that were reported by few studies. We also evaluated the mean difference in LVEF after unsuccessful CTO PCI if reported in the included studies. The numerical values of the outcomes were tabulated. Outcomes were reported at the longest available follow-up.

2.4 | Data synthesis and statistical analysis

Statistical analysis was conducted using Review manager software (Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Descriptive analyses were conducted using frequencies for categorical variables and standardized means with standard deviations (SD) for continuous variables. Summary results were presented as mean difference. Confidence intervals (CI) were calculated at 95% level for overall estimates effect. A standard, fixed-effects model (Mantel-Haenszel method) was used in the absence of heterogeneity among studies ($I^2 < 25\%$).[10] In the presence of heterogeneity, the DerSimonian and Laird random-effects model was used. Statistical heterogeneity across trials was assessed by I^2 statistics, with I^2 statistic values <25%, 25-50%, and >50% considered as low, moderate, and high degree of heterogeneity, respectively.[10] Tests were two-tailed and a *P*-value ≤0.05 was considered statistically significant. Weighted mean follow-up durations were calculated with the sample size being the weight. Potential publication bias was assessed by visual assessment of constructed funnel plots using Egger's test.[11]

Subgroup analysis was performed for the primary outcome comparing studies with mean baseline LVEF <50% versus those with mean baseline LVEF of 50% or higher. Further sensitivity analyses included studies that defined CTOs as occlusions of at least 3 month duration, and with follow-up period of at least 3 months, which has been proposed as the minimum time interval required for stunned and hibernating myocardium to recover after revascularization.[12]

3 | RESULTS

3.1 | Characteristics of the included studies and quality assessment

The study selection process is described in Figure 1. Our initial search yielded 827 citations. The characteristics of the included studies are described in (Table 1). Only one randomized-controlled trial (RCT) was identified.[7] Thirty-four observational studies [including two abstracts [13,14]] with a total of 2804 patients met our inclusion criteria.[13–46] Cardiac magnetic resonance imaging (CMR) was used to assess LVEF in nine studies[14–17,29,32,33,40,41] while echocardiography was used in 10 studies.[22,24,26,31,36,37,39,43–45] Other studies used left ventriculography[13,20,21,23,25,28,34,35,42,46] or nuclear imaging,[27,38] or did not specify the method used for assessing LVEF.[18,19,30] The

TABLE 1 Baseline characteristics of the patients that were included in the meta-analysis studies

Study	Year	Country of the study	Number of patients	Number of patients (Included in outcomes)	CTO duration	CTO TIMI flow	Duration of follow up (months mean)	Assessment of LVEF modality
Choi et al[19]	2017	South Korea	305	305	3 months	0	20	NR
Nakashi et al[36]	2017	Japan	59	59	3 months	0	8	ECHO
Sotomi et al[43]	2017	Japan	37	35	Unknown	0	3	ECHO
Stuijfzand et al[14]	2017	The Netherlands	69	69	Unknown	Unknown	3	CMR
Bucciarelli et al[15]	2016	UK	50	50	3 months	0	3	CMR
Cardona et al[16]	2016	Spain	32	29	3 months	?	6	CMR
Chadid et al[17]	2015	Germany	43	43	3 months	0	9	CMR
El shafey et al[24]	2015	Egypt	37	37	3 months	0 or 1	3	ECHO
Daniłowicz-Szymanowicz et al[22]	2014	Poland	23	23	4 weeks	Unknown	3	ECHO
Erdogan et al[26]	2013	Turkey	118	118	3 months	0 or 1	1	ECHO
Omura et al[13]	2013	Japan	168	168	Unknown	Unknown	6	left ventriculogram
Pujadas et al[40]	2013	Spain	33	33	3 months	0	6	CMR
Roifman et al[41]	2013	Canada	19	19	3 months	0 or 1	4	CMR
Kirschbaum et al[33]	2012	The Netherlands	43	43	3 months		6	CMR
Park et al[37]	2012	South Korea	58	58	1 month	0 or 1	6	ECHO
Sun et al[44]	2012	China	99	99	3 months	Unknown	12	ECHO
Chen et al[18]	2009	China	132	132	3 months	0	12	NR
Fiocchi et al[29]	2009	Italy	14	14	3 months	Unknown	6	CMR
Pavlovic et al[38]	2009	Serbia	20	20	3 months	0 or 1	11	Nuclear scan
Kirschbaum et al[32]	2008	The Netherlands	21	21	6 weeks	0	36	CMR
Valenti et al[45]	2008	Italy	290	290	3 months	0	6	ECHO
Ermis et al[27]	2005	USA	19	19	6 weeks	Unknown	1.5	Radionucleotide ventriculography
Fang et al[28]	2005	Taiwan	129	129	6 weeks	0	6	L Ventriculogram
Piscione et al[39]	2005	Italy	35	35	Unknown	Chronic occlusion	6	ECHO
Wener et al[46]	2005	Germany	119	119	2 weeks	0	4.9	L Ventriculogram
Chung et al[20]	2003	Taiwan	75	75	3 months	0 or 1	6	L Ventriculogram
Dzavik et al[23]	2001	Canada	139	139	6 weeks	0 or 1	6	L Ventriculogram
Jin et al[31]	2001	China	64	64	2 weeks	0	6	ECHO
Sirnes et al[42]	1998	Norway	95	95	Unknown	Unknown	6.7	L Ventriculogram
Danchin et al[21]	1996	France	55	55	10 days	0	6	L Ventriculogram
Mori et al[35]	1996	Japan	96	96	1 month	0 or 1	6	L Ventriculogram
Engelstein et al[25]	1994	Germany	49	49	3 weeks	0 or 1	2.5	L Ventriculogram
Ivanhoe et al[30]	1992	USA	242	175	10 days	0 or 1	6	NR
Melchior et al[34]	1987	Switzerland	20	20	Unknown	Unknown	9	L Ventriculogram

ECHO, echocardiogram; CMR, cardiac magnetic-resonance imaging; L ventriculogram, Left ventriculogram; NR, not reported.

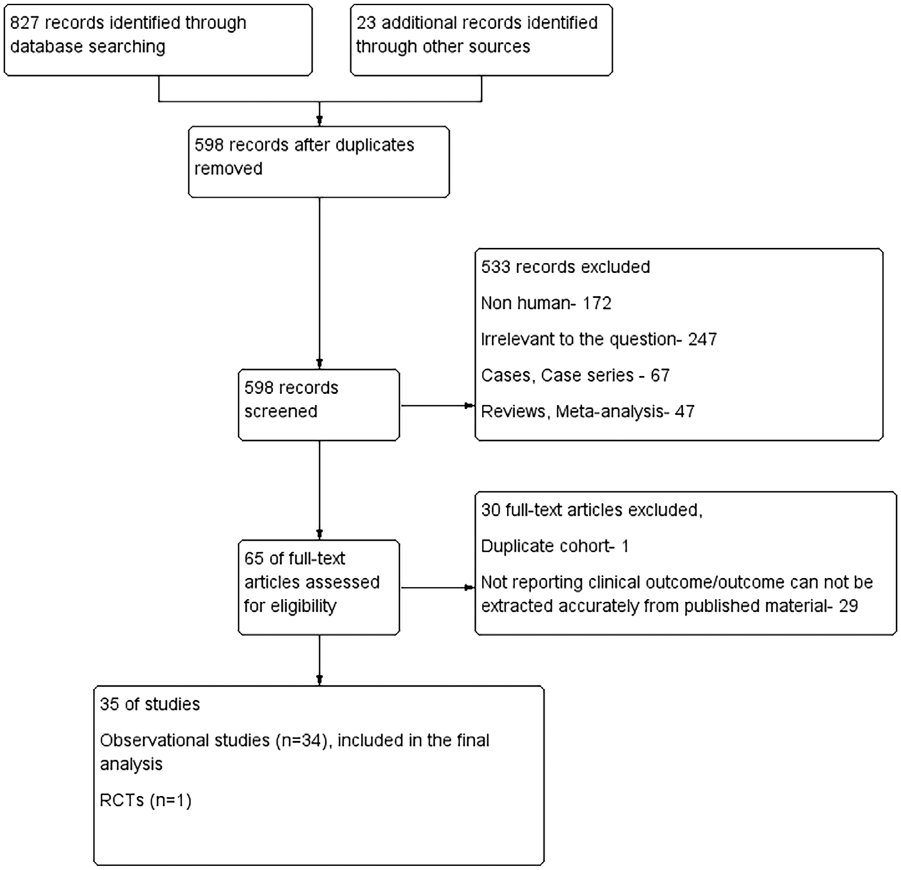


FIGURE 1 Flow diagram of the studies included in the meta-analysis

weighted mean follow-up period was 7.9 months. Four studies also reported the change in LVEF after failed CTO PCI.[18,33,40,41] All studies met the inclusion criteria with no evidence of publication bias (Supplementary Figures S1-S4). The risk of bias of the included studies, as assessed with the Newcastle-Ottawa scale is shown in Supplementary Table S1.

3.2 | Baseline characteristics of the included cohorts

The baseline patient characteristics are described in Table 2. Mean age was 61 ± 10 years and 80.6% of the patients were men. Approximately half of the patients had prior myocardial infarction (47%). The CTO target artery was the left anterior descending (LAD) in 43% and the right coronary (RCA) in 40% of patients. Baseline characteristics and demographics of patients in studies describing LVEF change after failed CTO PCI are described in (Supplementary Table S2).

3.3 | Outcomes

Successful CTO PCI was associated with a significant increase in LVEF (mean difference 3.8%, 95%CI 3.0-4.6, $P < 0.0001$, $I^2 = 45\%$) over a weighted mean follow-up of 7.9 months (Figure 2), while failed CTO PCI was not associated with a change in LVEF (4 studies, 70 patients)[18,33,40,41] (mean difference 2.2%, 95%CI −1.4, 5.8, $P = 0.24$) (Figure 3).

LVESV was analyzed in 10 studies including 502 patients.[15–17,24,26,29,36,38,40,44] Successful CTO PCI was associated with a significant decrease in LVESV (−4.0 mL, 95%CI −6.0, −2.1, $P < 0.0001$, $I^2 = 0\%$) (Figure 4). LVEDV was analyzed in nine studies including 403 patients.[15–17,24,26,29,36,38,40] Successful CTO PCI was not associated with a decrease in LVEDV (−2.2 mL, 95%CI −5.7 to 1.1, $P = 0.19$, $I^2 = 0\%$) (Figure 4).

In a subgroup analysis for the primary outcome comparing studies with documented baseline LVEF <50% versus those with baseline LVEF ≥50%, successful CTO PCI remained associated with improvement in LVEF in both groups (mean difference 5.0%, 95%CI 3.7, 6.2, $P < 0.0001$, $I^2 = 45\%$ and 2.6 %, 95%CI 1.8, 3.4, $P < 0.0001$, $I^2 = 2\%$), respectively. Successful CTO PCI was associated with greater improvement of LVEF in studies with LVEF <50% as compared with studies with LVEF ≥ 50% ($P = 0.003$) (Figure 5).

Furthermore, in a sensitivity analysis including only studies with documented CTO duration of at least 3 months and follow-up duration of at least 3 months after CTO PCI (15 studies, 1248 patients),[15–20,24,29,33,36,38,40,41,44,45] successful CTO PCI remained associated with significant improvement in LVEF (4.3%, 95%CI 3.0, 5.5, $P < 0.00001$).

TABLE 2 Demographics of the patients in the included studies

Study	Year	*N*	Male (%)	Age (Mean)	Smoking (%)	DM (%)	HTN (%)	Dyslipidemia (%)	prior MI (%)	CTO in LAD (%)	CTO in RCA (%)	CTO in LCX (%)
Choi et al	2017	305	75	62 ± 11	55.4	44.6	64.3	28.5	20.3	39	39.7	27.9
Nakashi et al	2017	69										
Sotomi et al	2017	59	90	66 ± 11	68	37	78	86	61	36	46	19
Stuijfzand et al	2017	37	78.4	65.6 ± 11.1	54.1	43.2	75.7	59.5	35.1			
Bucciarelli et al	2016	50	94	65 ± 9	69	22	66	72				
Cardona et al	2016	29	79	59 ± 10.2	34	31	47	53	56	41	37	22
Chadid et al	2015	37	94.5	57.25 ± 8					50	46.5	33.5	20
El shafey et al	2015	43	95.3	62.5 ± 9.6	60.5	30.2	79.1	79.1		37.2	41.9	20.9
Daniłowicz-Szymanowicz et al	2014	23	70.5	55 ± 7.5		43.5	66	100	60			
Erdogan et al	2013	168										
Omura et al	2013	118										
Pujadas et al	2013	33	79	66 ± 9.5	70	37	84	76	67			
Roifman et al	2013	19	74	62.4 ± 9.8	11	26	74	95	58	37	47	16
Kirschbaum et al	2012	43	79	60 ± 10	21	21	42	79	53			
Park et al	2012	58	82.8	59.9 ± 10.5	48.3	36.2	56.9	34.5	12.1	50	34.5	15.5
Sun et al	2012	99	91.933	54.47 ± 3.77	68.83333	24.6	35.933	30.5	65.03			
Chen et al	2009	132	74.2	63.92 ± 10.74	34.8	25.8	75.8	19.7	45.5			
Fiocchi et al	2009	14										
Pavlovic et al	2009	20	74.15	56 ± 5	0	16.5	71.5	86.5	100			
Kirschbaum et al	2008	21	86	63.7 ± 10.7	28.5	14.2	42.8	66.6	57.1	52.3	38	9.5
Valenti et al	2008	290										
Ermis et al	2005	19	84.2	58.3 ± 5.4					84.2			
Fang et al	2005	129	72.95	65.6 ± 11.5	37.3	41.65	61.15	64.7	37.1	41.1	37.15	21.75
Piscione et al	2005	35	87		26	18	13	26	100	50	27	23
Wener et al	2005	119										
Chung et al	2003	75	81.5	66.5 ± 9.5	40.5	40	57.5	25.5	50	47	53	
Dzavik et al	2001	64	71	61.85 ± 11.5	35.5	14	41	71.5	69.5	32.9	44.65	22.35
Jin et al	2001	139										
Sirnes et al	1998	95			21	8.4	24.2					
Danchin et al	1996	55	79.5	54.5 ± 10						52	48	
Mori et al	1996	96	85.65	59 ± 8.5		27	44	27.5	58.5	59	25.5	15.5
Engelstein et al	1994	49	83.5	52 ± 9.5					62	44	51.5	
Ivanhoe et al	1992	242										
Melchior et al	1987	20	85	53.25 ± 10.9					70			
Weighted mean		2804	80.6	61.22 ± 10.1	45.45	31.5	57.02	43.47	47.11	43.4	39.85	22.17

DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; CTO, chronic total occlusion.

4 | DISCUSSION

Our meta-analysis of 34 studies with 2804 patients demonstrates that successful CTO PCI is associated with statistically significant increase in mean LVEF by 3.8% during a mean follow-up duration of 7.9 months. This improvement was consistent in further sensitivity and subgroup analyses. Furthermore, successful CTO PCI was associated with statistically significant reduction in LVESV indicating an improvement in LV

Study or Subgroup	After CTO PCI Mean	SD	Total	Before CTO PCI Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bucciarelli et al 2016	67	12	50	62	13	50	2.1%	5.00 [0.10, 9.90]
cardona et 2016	37.7	8	29	31.3	7.4	29	2.8%	6.40 [2.43, 10.37]
Chadid et al 2015	51.5	10.8	43	49.1	10.4	43	2.4%	2.40 [-2.08, 6.88]
chen et al 2009	54	8	132	45	11	132	4.8%	9.00 [6.68, 11.32]
choi et al 2017	51.6	12.5	305	47.8	12.3	305	5.3%	3.80 [1.83, 5.77]
Chung et al 2003	57.44	17.93	75	53.28	16.004	75	1.8%	4.16 [-1.28, 9.60]
Danchin et al 1996	60.14	13.18	55	54.38	13.6	55	2.0%	5.76 [0.75, 10.77]
Danilowicz-Szymanowicz et al 2014	55.48	8.42	23	50.05	7.95	23	2.2%	5.43 [0.70, 10.16]
Dzavik et al 2001	62.5	11.6	139	62	11.5	139	4.2%	0.50 [-2.22, 3.22]
El shafey et al 2015	54.4	5.52	37	52.75	5.56	37	4.5%	1.65 [-0.87, 4.17]
Engelstein et al 1994	62.57	10.75	49	56.9	6.9	49	3.2%	5.67 [2.09, 9.25]
Erdogan et al 2013	58.32	10.2	118	56.31	9.81	118	4.4%	2.01 [-0.54, 4.56]
Ermis et al 2005	52.8	10.2	19	44.7	10.9	19	1.3%	8.10 [1.39, 14.81]
Fang et al 2005	58.77	15.76	129	56.2	16.19	129	2.8%	2.57 [-1.33, 6.47]
Fiocchi et al 2009	54.15	16.84	14	49.68	16.13	14	0.4%	4.47 [-7.74, 16.68]
Ivanhoe et al 1992	56	10	175	55	10	242	5.4%	1.00 [-0.94, 2.94]
Jin et al 2001	39.65	6.7	64	34.24	6.1	64	4.9%	5.41 [3.19, 7.63]
Kirschbaum et al 2008	63	11	21	60	9	21	1.5%	3.00 [-3.08, 9.08]
Kirschbaum et al 2012	54	12	43	50	11	43	2.1%	4.00 [-0.87, 8.87]
Melchior et al 1987	63	9	20	59	11	20	1.4%	4.00 [-2.23, 10.23]
Mori et al 1996	44.8	10.9	96	40.47	9.41	96	4.0%	4.33 [1.45, 7.21]
Nakashi et al 2017	56.1	10.6	59	54.2	12.1	59	2.7%	1.90 [-2.20, 6.00]
Omura et al 2013	56	13	168	55	13	168	4.1%	1.00 [-1.78, 3.78]
park et al 2012	60.1	8.3	58	57.3	9.9	58	3.4%	2.80 [-0.52, 6.12]
Pavlovic et al 2009	47.86	15.355	20	45.66	14.45	20	0.7%	2.20 [-7.04, 11.44]
Piscione et al 2005	48.7	8.11	35	41.7	8.11	35	2.9%	7.00 [3.20, 10.80]
Pujadas et al 2013	65	11.5	33	62	12.2	33	1.6%	3.00 [-2.72, 8.72]
Roifman et al 2013	54.3	10.7	19	50.3	12.6	19	1.1%	4.00 [-3.43, 11.43]
Sirnes et al 1998	67	11	95	62	13	95	3.3%	5.00 [1.58, 8.42]
sotomi et al 2017	59.2	15	35	57.7	15.9	37	1.1%	1.50 [-5.64, 8.64]
Stuijfzand et al 2017	47.5	11.4	69	46.4	11	69	3.0%	1.10 [-2.64, 4.84]
Sun et al 2012	51.2	7.638	99	46.8	9.34	99	4.7%	4.40 [2.02, 6.78]
Valenti et al 2008	46.5	11.3	290	42.2	12.1	290	5.4%	4.30 [2.39, 6.21]
Werner et al 2005	67	16	119	60	19	119	2.4%	7.00 [2.54, 11.46]
Total (95% CI)			**2735**			**2804**	**100.0%**	**3.84 [3.01, 4.67]**

Heterogeneity: Tau² = 2.34; Chi² = 59.50, df = 33 (P = 0.003); I² = 45%
Test for overall effect: Z = 9.09 (P < 0.00001)

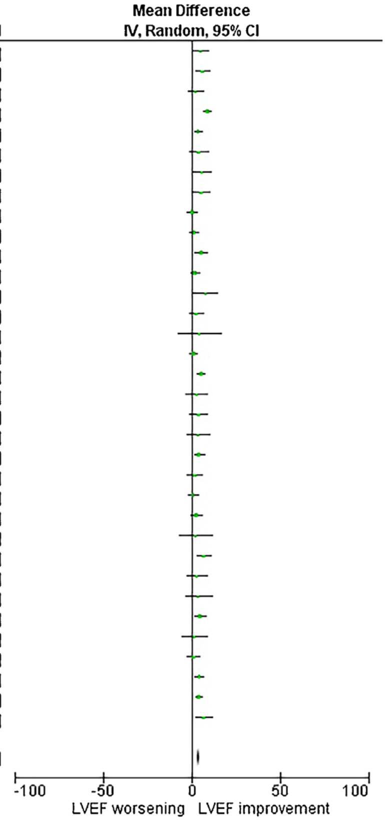


FIGURE 2 Forrest plot of studies evaluating the impact of successful CTO PCI on LVEF. The results are presented as mean LVEF difference after versus before successful CTO PCI. CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention

remodeling. Conversely, failed CTO PCI was not associated with improvement in LVEF.

Our results are in contrast with the results of the only randomized-controlled trial published to date examining the impact of CTO PCI on LV function and volume that did not demonstrate any difference between the CTO PCI and medical therapy only groups. Similarly, the Recovery of left ventricular function in Chronic total occlusion (REVASC) trial (presented at the TCT 2017 meeting, Denver, Colorado) randomized 205 patients to CTO PCI versus medical therapy alone and showed no difference in LVEF during a median follow-up of 6 month. Potential explanations for the discrepancy between observational and randomized studies include: (a) inclusion of patients with recent ST-segment elevation acute myocardial infarction in the EXPLORE trial; (b) inclusion of patients with 100% successful CTO recanalization in the observational studies, whereas CTO PCI success was 73% in EXPLORE; (c) short duration of follow-up (4 months in EXPLORE, 6 months in REVASC vs 7.9 months in the studies included in the meta-analysis studies). In patients with chronic ischemic LV dysfunction, improvement of dysfunctional but viable myocardium may not occur until after 3-6 months from revascularization.[12] However, Bondarenko et al studied the time course of functional recovery after revascularization of hibernating myocardium on 35 patients using contrast-enhanced CMR. Functional myocardial recovery started at 3-6 months with continuing improvement up to 24 months, suggesting that recovery of systolic function can be further delayed up to 24 months, especially in myocardial segments with higher extent of

Study or Subgroup	After CTO PCI Mean	SD	Total	Before CTO PCI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
chen et al 2009	46	5	20	42	16	20	25.0%	4.00 [-3.35, 11.35]
Kirschbaum et al 2012	47	13	29	46	16	29	24.0%	1.00 [-6.50, 8.50]
Pujadas et al 2013	63	9.4	10	57	8.8	10	21.2%	6.00 [-1.98, 13.98]
Roifman et al 2013	56.6	8	11	57.6	8.1	11	29.8%	-1.00 [-7.73, 5.73]
Total (95% CI)			**70**			**70**	**100.0%**	**2.21 [-1.46, 5.89]**

Heterogeneity: Chi² = 2.07, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)

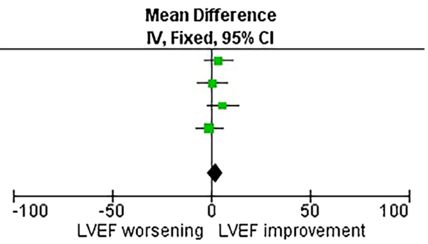
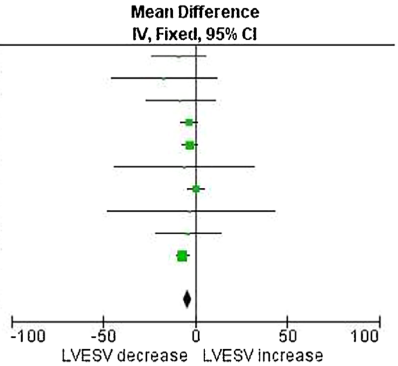


FIGURE 3 Forrest plot of studies evaluating the impact of failed CTO PCI LVEF. The results are presented as mean LVEF difference after versus before failed CTO PCI. CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention

Forrest plot of studies evaluating the impact of successful CTO PCI on LVESV.

Study or Subgroup	After CTO PCI Mean	SD	Total	Before CTO PCI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bucciarelli et al 2016	56	38	50	65	38	50	1.8%	-9.00 [-23.90, 5.90]
cardona et 2016	143	58	29	160	54	29	0.5%	-17.00 [-45.84, 11.84]
Chadid et al 2015	81	47	43	89	41	43	1.1%	-8.00 [-26.64, 10.64]
El shafey et al 2015	48.14	8.96	37	51.59	10.86	37	18.9%	-3.45 [-7.99, 1.09]
Erdogan et al 2013	31.63	16.22	118	34.54	16.49	118	22.4%	-2.91 [-7.08, 1.26]
Fiocchi et al 2009	85.53	52.35	14	91.6	50.05	14	0.3%	-6.07 [-44.01, 31.87]
Nakashi et al 2017	52.4	11.6	59	52.1	13.4	59	19.1%	0.30 [-4.22, 4.82]
Pavlovic et al 2009	127.53	75.45	20	130.03	70.96	20	0.2%	-2.50 [-47.89, 42.89]
Pujadas et al 2013	56	38.6	33	60	34.9	33	1.2%	-4.00 [-21.75, 13.75]
Sun et al 2012	58.25	11.43	99	65.32	12.64	99	34.6%	-7.07 [-10.43, -3.71]
Total (95% CI)			**502**			**502**	**100.0%**	**-4.09 [-6.06, -2.12]**

Heterogeneity: Chi² = 8.40, df = 9 (P = 0.49); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)



Forrest plot of studies evaluating the impact of successful CTO revascularization on LVEDV

Study or Subgroup	After CTO PCI Mean	SD	Total	Before CTO PCI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bucciarelli et al 2016	161	42	50	166	42	50	4.4%	-5.00 [-21.46, 11.46]
cardona et 2016	221	58	29	230	64	29	1.2%	-9.00 [-40.44, 22.44]
Chadid et al 2015	160	56	43	169	49	43	2.4%	-9.00 [-31.24, 13.24]
El shafey et al 2015	114.36	14.16	37	115.24	14.96	37	26.8%	-0.88 [-7.52, 5.76]
Erdogan et al 2013	71.98	22.64	118	76.22	22.55	118	35.5%	-4.24 [-10.01, 1.53]
Fiocchi et al 2009	163.78	10.7	14	162.31	9.62	14	20.8%	1.47 [-6.07, 9.01]
Nakashi et al 2017	99.1	38.8	59	102	40.1	59	5.8%	-2.90 [-17.14, 11.34]
Pavlovic et al 2009	210.86	84.81	20	218.33	83.69	20	0.4%	-7.47 [-59.69, 44.75]
Pujadas et al 2013	149	46.8	33	153	38.9	33	2.7%	-4.00 [-24.76, 16.76]
Total (95% CI)			**403**			**403**	**100.0%**	**-2.29 [-5.72, 1.15]**

Heterogeneity: Chi² = 2.27, df = 8 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)

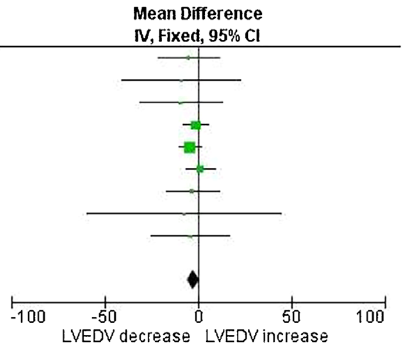


FIGURE 4 Forrest plot of studies evaluating the impact of successful CTO PCI on LVESV and LVEDV. The results as presented as mean LVESV/LVEDV difference after versus before CTO PCI. CTO, chronic total occlusion; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; PCI, percutaneous coronary intervention

hyperenhancement.[47] Detection of changes in LV function may, therefore, require long-term follow-up after revascularization particularly in CTO patients with higher ischemic burden and higher extent of hyperenhancement at baseline.

A previous meta-analysis of 34 studies with 2310 patients on the impact of CTO PCI on LV size and function was performed in 2015 by Hoebers et al and showed a statistically significant increase in LVEF (4.44%) and decrease in LVEDV index (6.14 mL/m^2) as compared with baseline.[48] The findings of our larger meta-analysis are consistent with the Hoebers meta-analysis on the impact of CTO PCI on LV ejection fraction, however we did not have enough data regarding LV end diastolic volume to detect the effect of successful CTO PCI. Our results reported the change in LVEDV not the LVEDV index as it is reported more frequently in the included studies. Our analysis included more recent studies including higher number of patients. We also included more studies using CMR for quantification of volumes.

The effect of CTO PCI on LVEF may be more pronounced in patients with depressed LVEF. Most studies excluded patients with severely depressed LV function. Our subgroup analysis comparing studies with baseline LVEF lower than 50% versus those with baseline LVEF ≥50% suggests that patients with lower LVEF tend to have larger improvement in LV systolic function (5.0% vs 2.6%, $P = 0.003$). Cardona et al in 2016 studied 29 patients with systolic heart failure and demonstrated 6.4% improvement in LVEF after successful CTO PCI, with concomitant improvement in New York Heart Association functional class, angina, and brain natriuretic peptide levels.[16] Moreover, subgroup analyses of other studies have shown that the most improvement of LVEF is achieved when baseline LVEF is below 50%.[13,17,19]

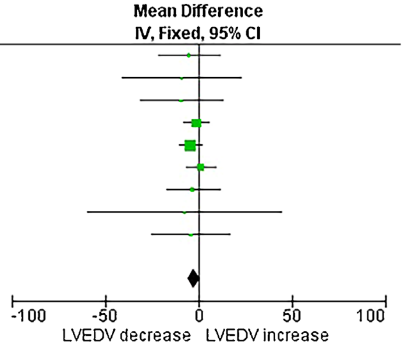
Some of the studies included in the meta-analysis defined "CTOs" as lesions with <3 months occlusion duration, which is the currently accepted threshold for a lesion to be characterized as CTO. When restricting our analyses to studies with documented CTO duration of at least 3 months and with follow up duration of at least 3 months significant improvement in LVEF was shown (4.31%, 95%CI [3.08, 5.55], $P < 0.00001$) in 1248 patients 15 studies.[15–20,24,29,33,36,38,40,41,44,45]

4.1 | Study limitations

Our study has important limitations. There was moderate degree of heterogeneity in our primary analysis. This could be explained by difference in cohort sizes, definition of CTO, CTO location, imaging modality and follow-up duration. However, we used random-effects

Study or Subgroup	After CTO PCI Mean	SD	Total	Before CTO PCI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bucciarelli et al 2016	161	42	50	166	42	50	4.4%	-5.00 [-21.46, 11.46]
cardona et 2016	221	58	29	230	64	29	1.2%	-9.00 [-40.44, 22.44]
Chadid et al 2015	160	56	43	169	49	43	2.4%	-9.00 [-31.24, 13.24]
El shafey et al 2015	114.36	14.16	37	115.24	14.96	37	26.8%	-0.88 [-7.52, 5.76]
Erdogan et al 2013	71.98	22.64	118	76.22	22.55	118	35.5%	-4.24 [-10.01, 1.53]
Fiocchi et al 2009	163.78	10.7	14	162.31	9.62	14	20.8%	1.47 [-6.07, 9.01]
Nakashi et al 2017	99.1	38.8	59	102	40.1	59	5.8%	-2.90 [-17.14, 11.34]
Pavlovic et al 2009	210.86	84.81	20	218.33	83.69	20	0.4%	-7.47 [-59.69, 44.75]
Pujadas et al 2013	149	46.8	33	153	38.9	33	2.7%	-4.00 [-24.76, 16.76]
Total (95% CI)			**403**			**403**	**100.0%**	**-2.29 [-5.72, 1.15]**

Heterogeneity: Chi² = 2.27, df = 8 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)



Study or Subgroup	After CTO PCI Mean	SD	Total	Before CTO PCI Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bucciarelli et al 2016	67	12	50	62	13	50	4.8%	5.00 [0.10, 9.90]
cardona et 2016	37.7	8	29	31.3	7.4	29	6.4%	6.40 [2.43, 10.37]
Chadid et al 2015	51.5	10.8	43	49.1	10.4	43	5.4%	2.40 [-2.08, 6.88]
chen et al 2009	54	8	132	45	11	132	11.5%	9.00 [6.68, 11.32]
choi et al 2017	51.6	12.5	305	47.8	12.3	305	12.9%	3.80 [1.83, 5.77]
Chung et al 2003	57.44	17.93	75	53.28	16.004	75	4.1%	4.16 [-1.28, 9.60]
El shafey et al 2015	54.4	5.52	37	52.75	5.56	37	10.7%	1.65 [-0.87, 4.17]
Fiocchi et al 2009	54.15	16.84	14	49.68	16.13	14	1.0%	4.47 [-7.74, 16.68]
Kirschbaum et al 2012	54	12	43	50	11	43	4.8%	4.00 [-0.87, 8.87]
Nakashi et al 2017	56.1	10.6	59	54.2	12.1	59	6.2%	1.90 [-2.20, 6.00]
Pavlovic et al 2009	47.86	15.355	20	45.66	14.45	20	1.6%	2.20 [-7.04, 11.44]
Pujadas et al 2013	65	11.5	33	62	12.2	33	3.7%	3.00 [-2.72, 8.72]
Roifman et al 2013	54.3	10.7	19	50.3	12.6	19	2.4%	4.00 [-3.43, 11.43]
Sun et al 2012	51.2	7.638	99	46.8	9.34	99	11.2%	4.40 [2.02, 6.78]
Valenti et al 2008	46.5	11.3	290	42.2	12.1	290	13.2%	4.30 [2.39, 6.21]
Total (95% CI)			**1248**			**1248**	**100.0%**	**4.31 [3.08, 5.55]**

Heterogeneity: Tau² = 2.05; Chi² = 23.74, df = 14 (P = 0.05); I² = 41%
Test for overall effect: Z = 6.85 (P < 0.00001)

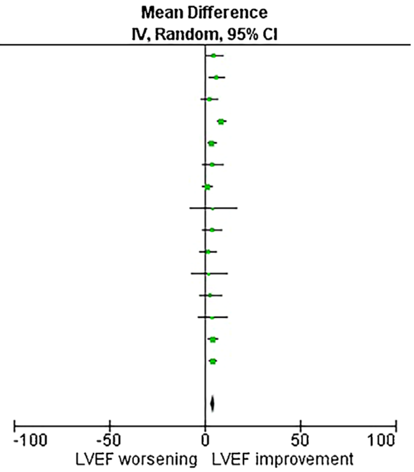


FIGURE 5 Forrest plot of subgroup analysis of studies with baseline LVEF <50% versus studies with baseline LVEF 50% or more evaluating the impact of successful CTO PCI on LVEF. The results as presented as mean LVEF difference after versus before CTO PCI. CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention

model and performed multiple sensitivity and subgroup analyses that provided consistent results. Second, it is possible that the improvement of LVEF after successful CTO PCI may result from appropriate medical therapy, yet in our analysis, failed CTO PCI was not associated with significant improvement in LVEF. However, the number of studies documenting LVEF before and after the failed procedure was limited (only 4 studies including 70 patients) in comparison with studies describing successful procedures (34 studies, 2735 patients). Third, there is a possibility that inter-observer variability in evaluating LVEF before and after revascularization could have affected our results. Finally, we did not evaluate clinical outcomes after successful CTO PCI. In patients with ischemic cardiomyopathy, Cioffi et al[15] demonstrated that reverse cardiac remodeling was associated with lower mortality (3%) compared with no reversal (22%).[49] Moreover, In the V-HeFT I and II studies, A 5% increase in ejection fraction was the best predictor of mortality.[50] However, the clinical implications of the 3.8% increase in LVEF and 4 mL decrease in LVESV remain unclear.

5 | CONCLUSIONS

Successful CTO PCI is associated with a statistically significant improvement in LV ejection fraction and decrease in LV end systolic volume, suggesting a beneficial effect of CTO recanalization on LV systolic function and remodeling. More pronounced improvement in LV ejection fraction is achieved in patients with lower baseline LVEF. An extended follow up period might be required to detect further improvement in systolic function after successful CTO recanalization. The clinical implications of these findings warrant further investigation.

DISCLOSURES

Michael Megaly, Marwan Saad, Peter Tajti, MD, M. Nicholas Burke, MD, Ivan Chavez, MD, Mario Gössl, MD, PhD, Daniel Lips, MD, Michael Mooney, MD, Anil Poulose, MD, Jay Traverse, MD, Yale Wang, MD, Louis P. Kohl, MD, and Steven M. Bradley, MD, MPH, have nothing to disclose. Paul Sorajja, MD, consulting, speaking for Abbott, Edwards, Medtronic, and BSCI. Emmanouil Brilakis: consulting/speaker honoraria from Abbott Vascular, ACIST, American Heart Association (associate editor Circulation), Amgen, Asahi, Cardiovascular Innovations Foundation (Board of Directors), CSI, Elsevier, GE Healthcare, and Medtronic; research support from Boston Scientific and Osprey. Shareholder: MHI Ventures. Board of Trustees: Society of Cardiovascular Angiography and Interventions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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