Supplemental Appendix.

Supplemental Table 1. Medline Search Strategy

#	Search	Results
#1	("Coronary Occlusion"[Mesh] Or "Chronic total occlusion" [tiab] OR "CTO" [tiab])	4203
#2	("Percutaneous Coronary Intervention"[Mesh] OR "PCI"[Tiab] OR "Drug-Eluting Stents"[Mesh] OR "Optimal medical therapy"[tiab] OR "OMT " [TW] OR " Medical therapy" [tiab])	83438
#3	("Follow-Up Studies"[Mesh] OR Prospective Studies [Mesh] OR Retrospective Studies [Mesh] OR "Cohort Studies"[Mesh] OR "Registries"[Mesh] OR"Observational Study" [Pt] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial [ti] NOT (animals[mh] NOT humans [mh]))	2614142
#4	#1 AND #2 AND #3	784

Supplemental Table 2. Embase database search strategy:

#	Search	Results
#1	Coronary Occlusion.mp. or exp coronary artery occlusion/	12676
#2	Chronic total occlusion.m_titl.	1993
#3	exp percutaneous coronary intervention/	87104
#4	Drug-Eluting Stents.mp. or exp drug eluting stent/	29965
#5	exp prospective study/	445880
#6	Retrospective Studies.mp. or exp retrospective study/	651485
#7	Cohort Studies.mp.	28513
#8	Registries.mp. or exp register/	129908
#9	exp observational study/	138221
#10	(randomized controlled trial or controlled clinical trial).pt. or randomized.ti. or randomized.tw. or clinical trials as topic.kw.	625718
#11	#1 OR #2	13845
#12	#3 OR #4	103378
#13	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1845576
#14	#11 AND #12 AND #13	772

Supplemental Table 3. Scopus Search Strategy

#	Searches	Results
#1	KEY (coronary AND occlusion) OR TITLE-ABS-KEY (chronic AND total AND occlusion)	21,325
#2	KEY(Percutaneous Coronary Intervention) OR TITLE-ABS-KEY(PCI) OR TITLE-ABS-KEY(drug eluting stent)	75,662
#3	KEY(observational studies) OR KEY(cohort studies) OR KEY(prospective studies) OR KEY(restrospective studies) OR KEY(registeries) OR KEY(randomized controlled trial) OR TITLE-ABS-KEY(controlled clinical trial) OR KEY(randomized))	1,721,535
	#1 AND #2 AND #3	1394
#4	(LIMIT-TO (LANGUAGE,"English ")	1368
#5	(LIMIT-TO (DOCTYPE,"ar"))	1080
#6	(LIMIT-TO (SUBJAREA,"MEDI"))	1062
#7	(LIMIT-TO (SRCTYPE,"j"))	1062

Supplemental Table 4. Cochrane Central Register of controlled trials search strategy

#	Search	Results
#1	MeSH descriptor: [Coronary Occlusion] explode all trees	90
#2	"chronic total occlusion":ti,ab,kw (Word variations have been searched)	252
#3	CTO:ti,ab,kw (Word variations have been searched)	214
#4	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees	5312
#5	"PCI":ti,ab,kw (Word variations have been searched)	4698
#6	MeSH descriptor: [Drug-Eluting Stents] explode all trees	1412
#7	MeSH descriptor: [Follow-Up Studies] explode all trees	56055
#8	MeSH descriptor: [Prospective Studies] explode all trees	85152
#9	MeSH descriptor: [Retrospective Studies] explode all trees	9789
#10	MeSH descriptor: [Cohort Studies] explode all trees	141536
#11	MeSH descriptor: [Registries] explode all trees	1056
#12	observational studies:pt (Word variations have been searched)	774
#13	randomized controlled trial:pt (Word variations have been searched)	445768
#14	controlled clinical trial:ti,ab,kw (Word variations have been searched)	360114
#15	randomized:ti,ab,kw (Word variations have been searched)	579323
#16	MeSH descriptor: [Clinical Trials as Topic] explode all trees	57968
#17	"randomly":ti,ab,kw (Word variations have been searched)	170797
#18	MeSH descriptor: [Animals] explode all trees	8756
#19	MeSH descriptor: [Humans] explode all trees	379
#20	#1 or #2 or #3	369
#21	#4 or #5 or #6	8626
#22	#7 or #8 or #9 or #10 or #11 or #12 or #13 or 14 or #15 or #16 or #17 not (#18 not #19)	832444
#23	#20 and #21 and #22	145
#24	After Excluding reviews 142	142

Supplemental Table 5. Egger's test to asses for potential publication bias.

Outcome	Egger's regression intercept	95% CI	P value
All-cause mortality	0.02	-1.6 — 1.6	0.9
MACE	-0.26	-5.3 — 4.7	0.9
Recurrent MI	-0.62	-3.2 — 2.0	0.6
Repeated revascularization	-0.43	-6.7 — 5.9	0.9
Cardiac mortality	0.52	-2.6— 3.7	0.6

CI; confidence interval, MACE; major adverse cardiac events, MI; myocardial infarction.

Supplemental Table 6. Bias risk assessment of the included randomized controlled trials.

Study name	Random sequence generation	Allocation concealment	Blind participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective reporting
DECISION-CTO [1]	Low risk *	Low risk *	Low risk *	Low risk *	Low risk	Low risk
EURO-CTO [2]	Low risk	Low risk	Low risk *	Low risk	Low risk	Low risk
REVASC [3]	Low risk	Low risk	Low risk*	Low risk	Low risk	Low risk

*All the trials were open-label, however we believe that the lack of blinding is less likely to introduce bias on our outcomes of interest.

Supplemental Table 7. Bias risk assessment of the included observational studies.

Study name	Clear definition of study population	Clear definition of outcome and outcomes assessment	Independent assessment of outcome parameters	Sufficient duration of follow up	No selective loss during follow up	Important confounders and prognostic factors identified
ITALIAN Registry [4]	Yes	Yes	Yes	Yes	Yes	Yes‡
Choi [5]	Yes	Yes	Unclear	Yes	Yes	Yes‡
Guo [6]	Yes	Yes	Unclear	Yes	Yes	Yes‡
Ladwiniec [7]	Yes	Yes	Unclear	Yes	Yes	Yes‡
Yang [8]	Yes	Yes	Unclear	Yes	Yes	Yes‡

‡ Although all studies reported clinical outcomes in the matched populations, there might be residual or unmeasured confounders.

Supplemental Table 8. Assessment of the quality of evidence of the included randomized controlled trials using GRADE method

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	OMT	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 1 years to 5 years)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	18/777 (2.3%)	23/639 (3.6%)	**OR 0.700** (0.364 to 1.346)	**11 fewer per 1,000** (from 23 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Recurrent myocardial infraction (follow up: range 1 years to 5 years)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	46/777 (5.9%)	31/639 (4.8%)	**OR 1.312** (0.850 to 2.027)	**17 more per 1,000** (from 8 fewer to 54 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Repeated Revascularization (follow up: range 1 years to 5 years)												
3	randomised trials	not serious	serious [b]	not serious	serious [a]	none	58/777 (7.4%)	67/639 (10.4%)	**OR 0.566** (0.207 to 1.547)	**46 fewer per 1,000** (from 87 fewer to 52 more)	⨁⨁◯◯ LOW	CRITICAL
Stroke (follow up: range 1 years to 5 years)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	8/676 (0.1%)	11/535 (2.0%)	**OR 0.472** (0.165 to 1.354)	**20 fewer per 1,000** (from 33 fewer to 13 more)	⨁⨁⨁◯ MODERATE	CRITICAL
MACE (follow up: range 2 years to 5 years)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	112/777 (14.4%)	115/639 (17.9%)	**OR 0.709** (0.374 to 1.342)	**43 fewer per 1,000** (from 97 fewer to 45 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cardiac Mortality (follow up: range 1 years to 5 years)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	10/676 (1.4%)	14/535 (2.6%)	**OR 0.607** (0.261 to 1.414)	**10 fewer per 1,000** (from 19 fewer to 10 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; OR: Odds ratio; MACE; Major adverse cardiac events. Explanations; a. Wide confidence interval and small number of events, b. Confidence interval are not overlapping.

Supplemental Table 9. Assessment of the quality of evidence of the included observational studies using GRADE method

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Percutaneous coronary intervention	Optimal medical therapy	Relative (95% CI)	Absolute (95% CI)		
Cardiac Mortality (follow up: range 1 years to 5 years)												
5	observational studies	serious [a]	not serious*	not serious	not serious	none	65/1584 (4.1%)	101/1584 (6.4%)	**RR 0.635** (0.406 to 0.994)	**23 fewer per 1,000** (from 38 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Recurrent MI (follow up: range 1 years to 5 years)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	23/1390 (1.7%)	38/1390 (2.7%)	**OR 0.624** (0.314 to 1.242)	**10 fewer per 1,000** (from 19 fewer to 6 more)	⊕◯◯◯ VERY LOW	CRITICAL
Stroke (follow up: range 1 years to 5 years)												
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	3/777 (0.4%)	5/777 (0.6%)	**OR 0.622** (0.140 to 2.753)	**2 fewer per 1,000** (from 6 fewer to 11 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repeated Revascularization (follow up: range 1 years to 5 years)												
4	observational studies	serious [a]	serious [c]	not serious	serious	none	181/1065 (17.0%)	154/1065 (14.5%)	**OR 1.502** (0.745 to 3.029)	**58 more per 1,000** (from 33 fewer to 194 more)	⊕◯◯◯ VERY LOW	CRITICAL
All-cause Mortality (follow up: range 1 years to 5 years)												
3	observational studies	serious [a]	not serious	not serious	not serious [b]	none	99/958 (10.3%)	158/985 (16.0%)	**OR 0.585** (0.446 to 0.768)	**60 fewer per 1,000** (from 82 fewer to 32 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
MACE (follow up: range 1 years to 5 years)												
4	observational studies	serious [a]	serious [c]	not serious	serious [b]	none	170/1390 (12.2%)	224/1390 (16.1%)	**OR 0.814** (0.445 to 1.491)	**26 fewer per 1,000** (from 82 fewer to 62 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; MACE: Major adverse cardiac events. Explanations; a. This outcome is driven from observational studies, b. The confidence interval is wide, c. Confidence intervals of the studies are not overlapping.

Supplemental Table 10. Definition of myocardial infarction in each study

Study	Definition of myocardial infarction
DECISION-CTO [1]	NA
EURO-CTO [2]	The new universal definition of MI: detection of a rise of cardiac biomarker values [preferably cardiac troponin with at least one value above the 99th percentile upper reference limit combined with either symptoms of ischaemia, new or presumed new significant ST-segment T-wave changes, new left bundle branch block, development of pathological Q-waves in the ECG, new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.
REVASC [3]	NA
ITALIAN Registry [4]	CK-MB enzyme elevation >3 times the upper limit of the normal value, with or without the presence of new pathological Q waves, in 12-lead ECG. CK-MB were evaluated 6 h after the procedure and until normalization if the levels were abnormal.
Choi [5]	NA
Guo [6]	An increase in the concentration of CK-MB fraction or troponin-T/troponin-I greater than the upper limit of normal with concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia
Ladwiniec [7]	NA
Yang [8]	Recurrent symptoms with new ECG changes compatible with MI or cardiac marker level at least twice the upper limit of normal.

NA; not available, MI; myocardial infarction, ECG; electrocardiogram, CK; creatine kinase.

Supplemental Table 11. Definition of major adverse cardiac events in each study

Study	Major adverse cardiac events definition
DECISION-CTO [1]	A composite point of death, MI, Stroke, Any repeat revascularization.
EURO-CTO [2]	A composite point of death, MI, Stroke, Any repeat revascularization.
REVASC [3]	A composite point of all-cause death, MI, revascularization.
ITALIAN Registry [4]	A composite point of cardiac death, stroke, and AMI.
Choi [5]	A composite of total death, MI, and TVR.
Guo [6]	A composite of cardiac death, recurrent MI, and repeated revascularization.
Ladwiniec [7]	NA
Yang [8]	A composite of cardiac death, recurrent MI, and any revascularization

MI; myocardial infarction, AMI; acute myocardial infarction, TVR; target vessel revascularization, NA; not applicable.

Supplemental Table 12. Inclusion and exclusion criteria of the included studies

Study	Inclusion criteria
DECISION-CTO [1]	Patients with angina or silent ischemia and documented ischemia; De novo lesion CTO; Reference vessel size 2.5 mm by visual estimation; At least one CTO lesions located in proximal or mid epicardial coronary artery. (If the patient has two CTO lesions, one CTO lesion should be located in proximal or mid epicardial coronary artery)
EURO-CTO [2]	Symptomatic patients with at least one CTO in a major coronary artery with a vessel diameter of at least 2.5 mm; Patients with a prior acute coronary syndrome were included only, if this event was related to a non-CTO lesion successfully treated more than 4 weeks before enrolment.
REVASC [3]	CTO of a native coronary artery with an estimated reference vessel diameter of 2.5 to 4.0 mm; CTO has more than 4 weeks duration; the target vessel has not previously been treated with percutaneous coronary intervention; the target vessel must be feasible for stent implantation; patient has stable or unstable angina pectoris or a positive functional study for ischemia.
ITALIAN Registry [4]	All comers; patients showing at coronary angiography ≥1 CTO in a main coronary artery (vessel size ≥2.5 mm).
Choi [5]	All-comers; at least 1 CTO lesion in the epicardial vessel and 2 or 3 rentrop collateral grade flow1 confirmed by a diagnostic angiography.
Guo [6]	≥1 CTO detected on diagnostic coronary angiography; symptomatic angina and/or functional ischemia.

Study	Inclusion criteria
Ladwiniec [7]	All-comers.
Yang [8]	One or more CTO lesions detected on diagnostic coronary angiography; symptomatic angina and/or a positive functional ischemia study.
Study	**Exclusion criteria**
DECISION-CTO [1]	History of bleeding diathesis or coagulopathy; Three vessel CTO; STEMI requiring primary stenting; Characteristics of lesion 1) Left main disease 2) In-stent restenosis 3) Graft vessels 4) Distal epicardial coronary artery CTO lesions; Left ventricular ejection fraction; Non-cardiac co-morbid conditions are present with limited life expectancy or that may result in protocol non-compliance (per site investigator's medical judgment).
EURO-CTO [2]	Patients were not enrolled if they had any exclusion criteria for implantation of a drug-eluting stent (e.g. patients not tolerating dual antiplatelet therapy or need for elective non-cardiac surgery within 6 months)
REVASC [3]	A documented left ventricular function < 30%; patient has AMI; patient has suffered a cerebrovascular accident or transient ischemic attack within the past 6 months; the target vessel or lesson shows angiographic evidence of severe calcification.
ITALIAN Registry [4]	A prior CABG procedure or a life expectancy <1 year represented.
Choi [5]	A prior CABG procedure.

Study	Exclusion criteria
Guo [6]	Underwent failed CTO-PCI; Previous CABG, for the reason that patients who have previously undergone CABG develop ischemia symptoms that can't be controlled by OMT; History of cardiogenic shock or cardiopulmonary resuscitation; STEMI during the preceding 48 h; Underwent CABG in the previous 30 days.
Ladwiniec [7]	Patients treated for AMI in the territory of the occluded vessel in the preceding three months, with prior CABG, mitral or aortic valve disease of moderate severity or greater.
Yang [8]	Previous history of CABG; cardiogenic shock or cardiopulmonary resuscitation as initial presentation; STEMI during the preceding 48h.

CTO; chronic total occlusion, AMI; acute myocardial infarction, CABG; coronary artery bypass grafting, LVEF; left ventricular ejection fraction, MI; myocardial infarction, PCI; percutaneous coronary intervention, OMT, optimal medical therapy; STEMI; ST-elevation myocardial infarction.

Supplemental Table 13. Meta-regression analysis of our outcomes of interest against age, diabetes mellitus, left anterior descending vessel, non-left anterior descending vessel and multiple vessel disease.

Variable	Outcome	Meta-regression coefficient	95 % CI	P value
Age	Cardiac mortality	-0.12	-0.34 — 0.10	0.18
	MACE	-0.20	-0.37 — -0.03	0.02
	Recurrent MI	-0.20	-0.38 — 0.02	0.02
	Repeated revascularization	-0.29	-0.72 — 0.13	0.16
	All-cause mortality	-0.06	-0.49 — 0.36	0.75
Diabetes mellitus	Cardiac mortality	-0.007	-0.08 — 0.06	0.84
	MACE	0.005	-0.05 — 0.07	0.87
	Recurrent MI	-0.03	-0.11— 0.05	0.49
	Repeated revascularization	-0.01	-0.07 — 0.08	0.87
	All-cause mortality	-0.01	-0.07 — 0.03	0.49
LAD	Cardiac mortality	0.0008	-0.09— 0.09	0.98
	MACE	0.04	-0.01 — 0.11	0.08
	Recurrent MI	0.04	-0.03 — 0.12	0.23
	Repeated revascularization	0.06	-0.01— 0.12	0.07
	All-cause mortality	0.006	-0.04— 0.05	0.8

Variable	Outcome	Meta-regression coefficient	95 % CI	P value
Non-LAD	Cardiac mortality	0.01	-0.02 — 0.05	0.38
	MACE	-0.01	-0.05 — 0.02	0.48
	Recurrent MI	-0.02	-0.08 — 0.04	0.50
	Repeated revascularization	-0.01	-0.07 — 0.04	0.47
	All-cause mortality	-0.003	-0.02 — 0.02	0.77
Multivessel disease	Cardiac mortality	-0.03	0.04 — -0.11	0.35
	MACE	-0.008	-0.05 — 0.04	0.69
	Recurrent MI	-0.02	-0.13 — 0.08	0.61
	Repeated revascularization	-0.006	-0.05 — 0.04	0.80
	All-cause mortality	-0.06	-0.12 — 0.07	0.62

CI; confidence interval, MACE; major adverse cardiac events, MI; myocardial infarction, NA; not available, LAD; left anterior descending artery, non-LAD; non-left anterior descending artery.

Supplemental Table 14. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3 and 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4 and 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplemental Tables 6, 7, and 8.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 and supplemental Figure 2.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2.
Risk of bias across	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental Figure 1 and

studies			supplemental Table 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 2, supplemental figures 3, 4, 5, and 6.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8 and 9
Section/topic	**#**	**Checklist item**	**Reported on page #**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding (Page 12)

References:

1. Lee SW, Lee PH, Ahn JM, et al. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. Circulation. 2019;139:1674-83.

2. Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. Eur Heart J. 2018;39:2484–93.

3. Mashayekhi K, Nuhrenberg TG, Toma A, et al. A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion: The REVASC Trial. JACC Cardiovasc Interv. 2018;11:1982-91.

4. Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. Eur Heart J. 2015;36:3189-98.

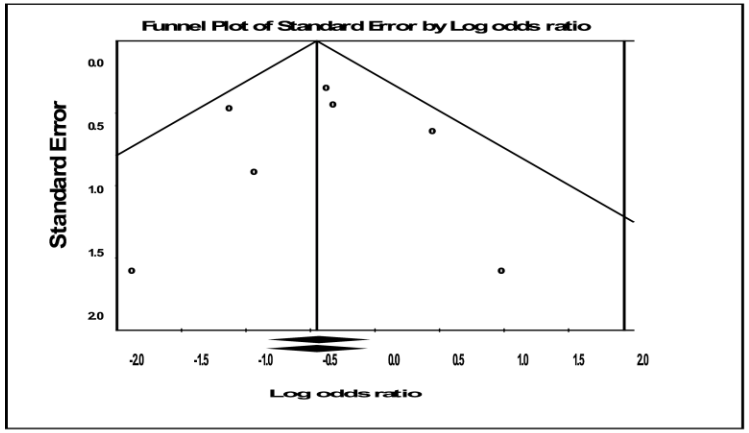
5. Choi SY, Choi BG, Rha S, et al. Percutaneous Coronary Intervention Versus Optimal Medical Therapy for Chronic Total Coronary Occlusion With Well-Developed Collaterals. J Am Heart Assoc. 2017;6:e006357.

6. Guo L, Zhong L, Chen K, Wu J, Huang RC. Long-term clinical outcomes of optimal medical therapy vs. successful percutaneous coronary intervention for patients with coronary chronic total occlusions. Hellenic J Cardiol. 2018;59:281-7.

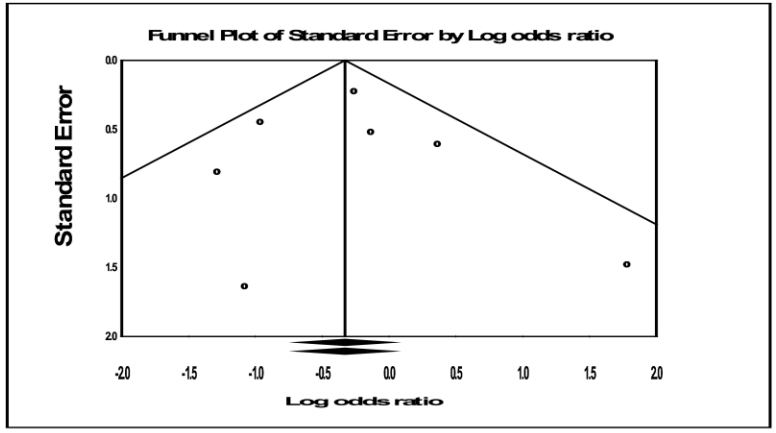
7. Ladwiniec A, Allgar V, Thackray S, Alamgir F, Hoye A. Medical therapy, percutaneous coronary intervention and prognosis in patients with chronic total occlusions. Heart. 2015;101:1907-14.

8. Yang JH, Kim BS, Jang WJ, et al. Optimal Medical Therapy vs. Percutaneous Coronary Intervention for Patients With Coronary Chronic Total Occlusion - A Propensity-Matched Analysis. Circ J. 2016;80:211-7.

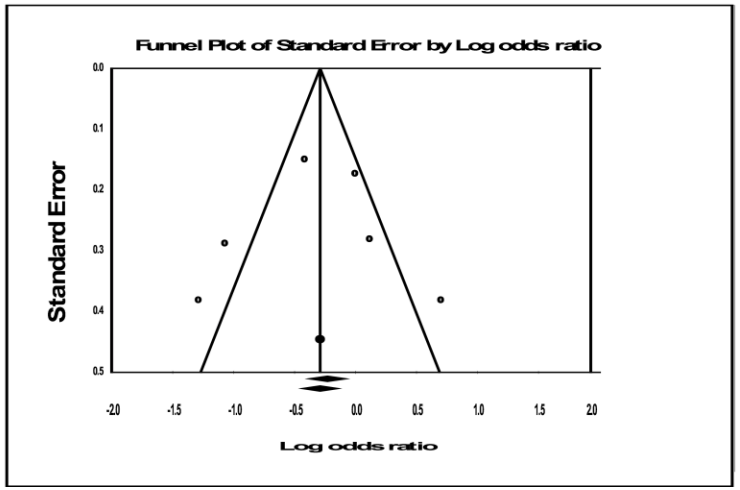
A) Cardiac Mortality



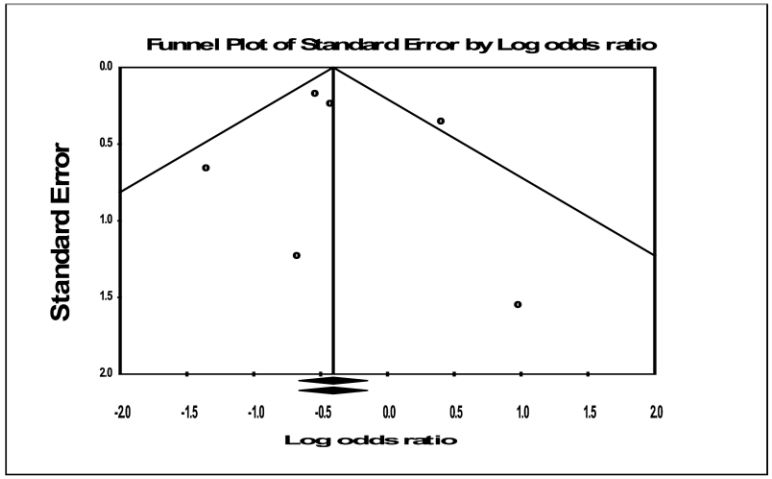
B) Recurrent Myocardial Infarction



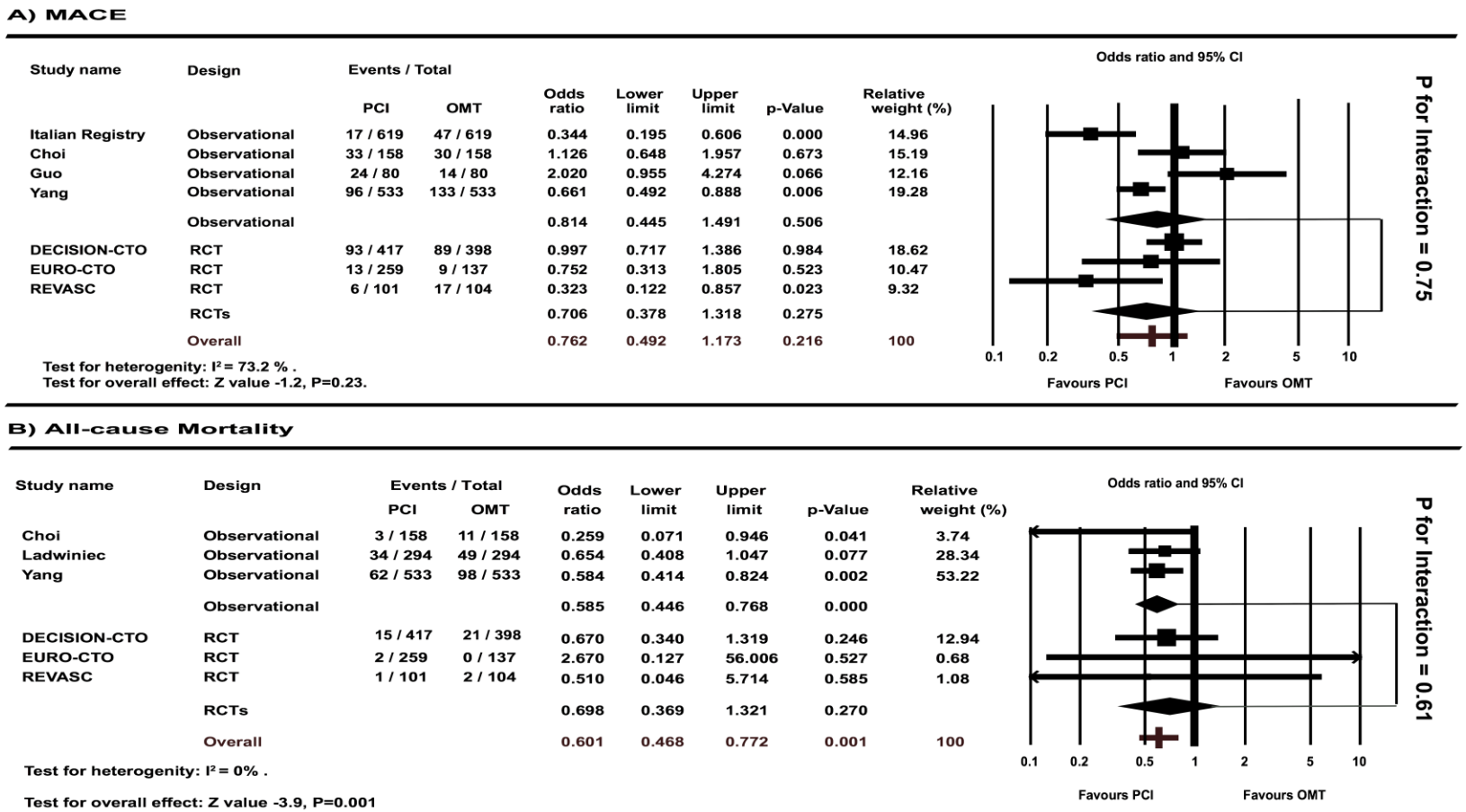
C) MACE



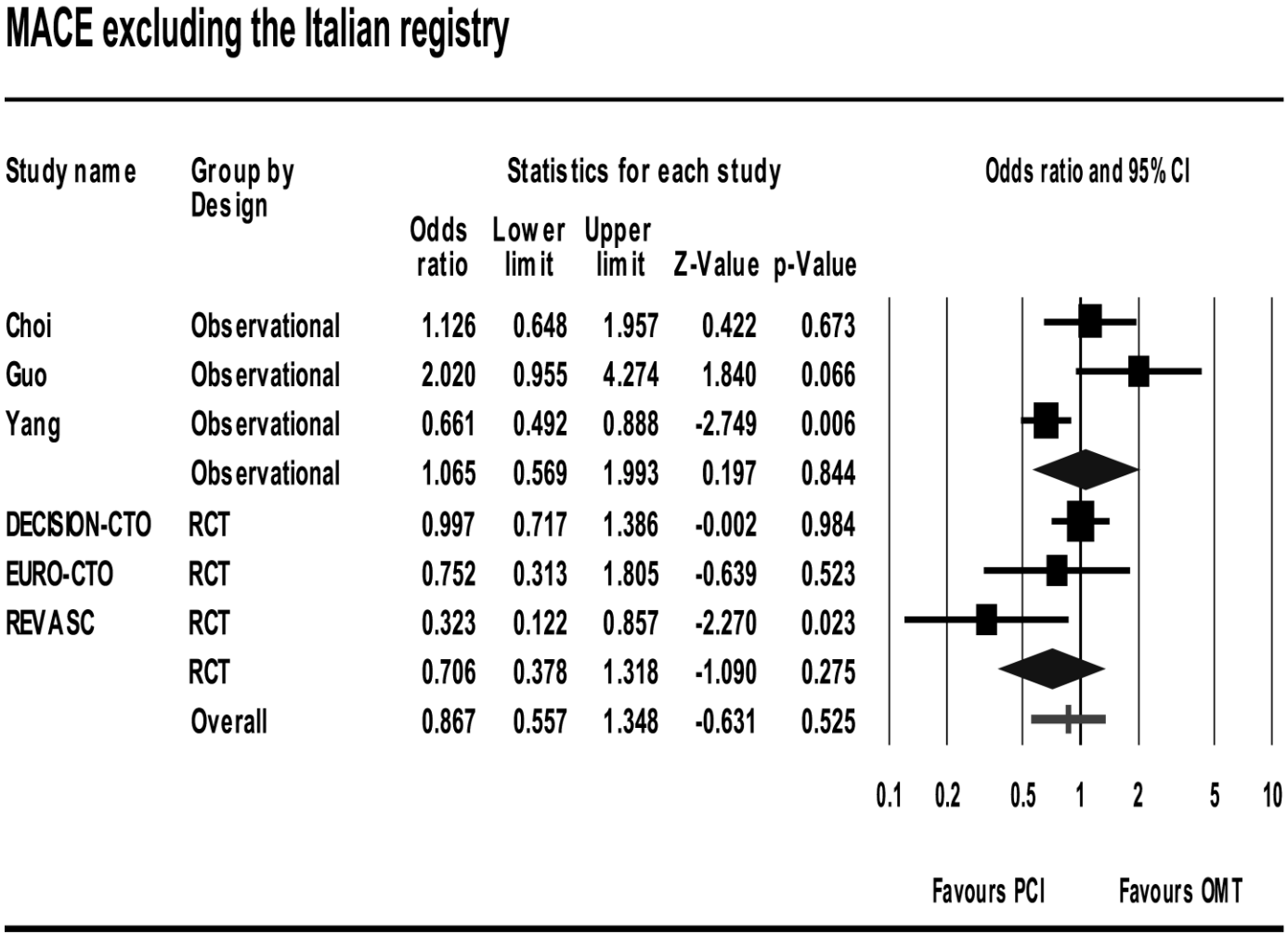
D) All-cause Mortality



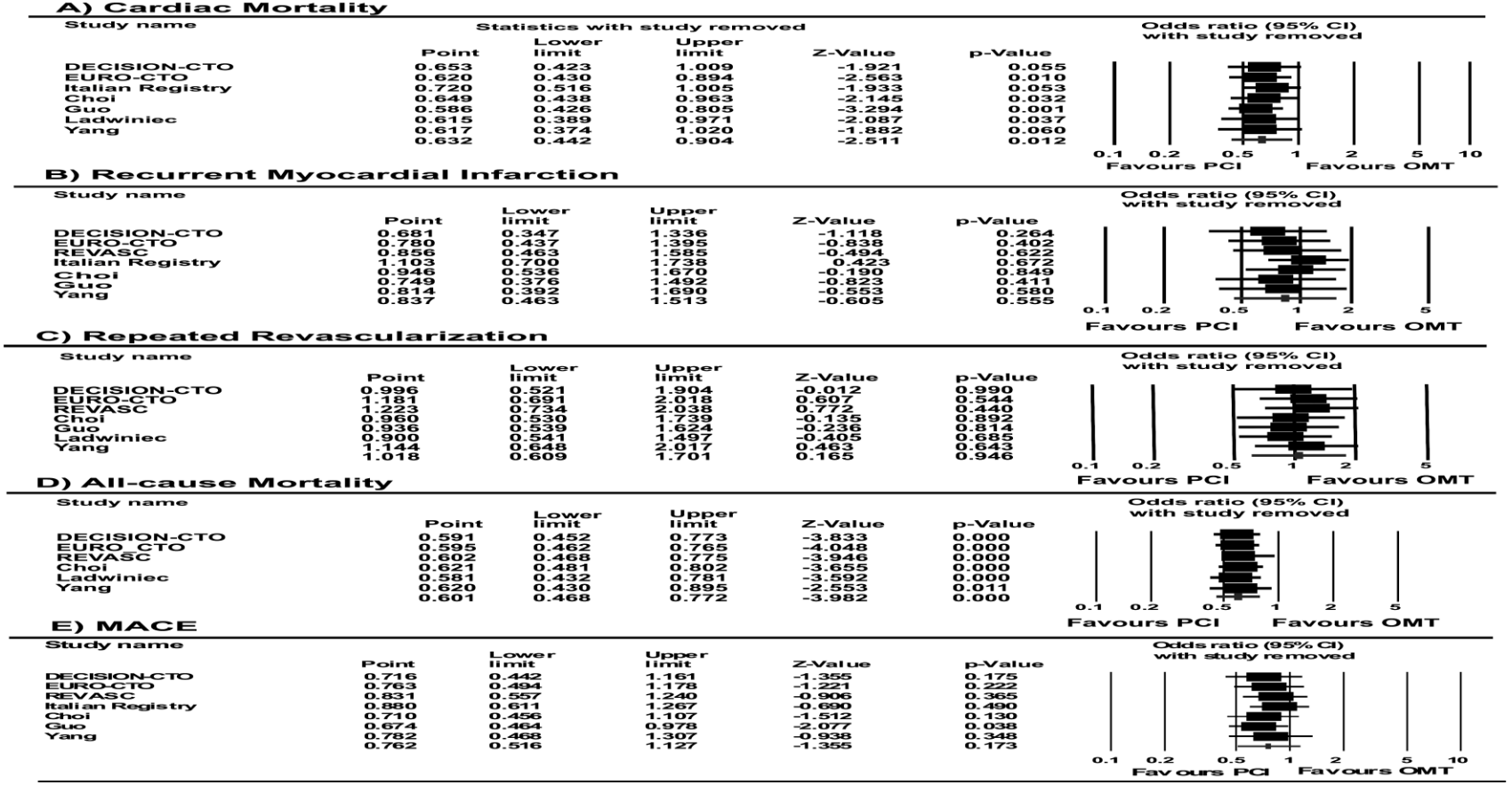
Supplemental Figure 1. Funnel plots of odds ratios and standard errors to assess for publication bias in cardiac mortality, recurrent myocardial infarction, major adverse cardiac events, and all-cause mortality.



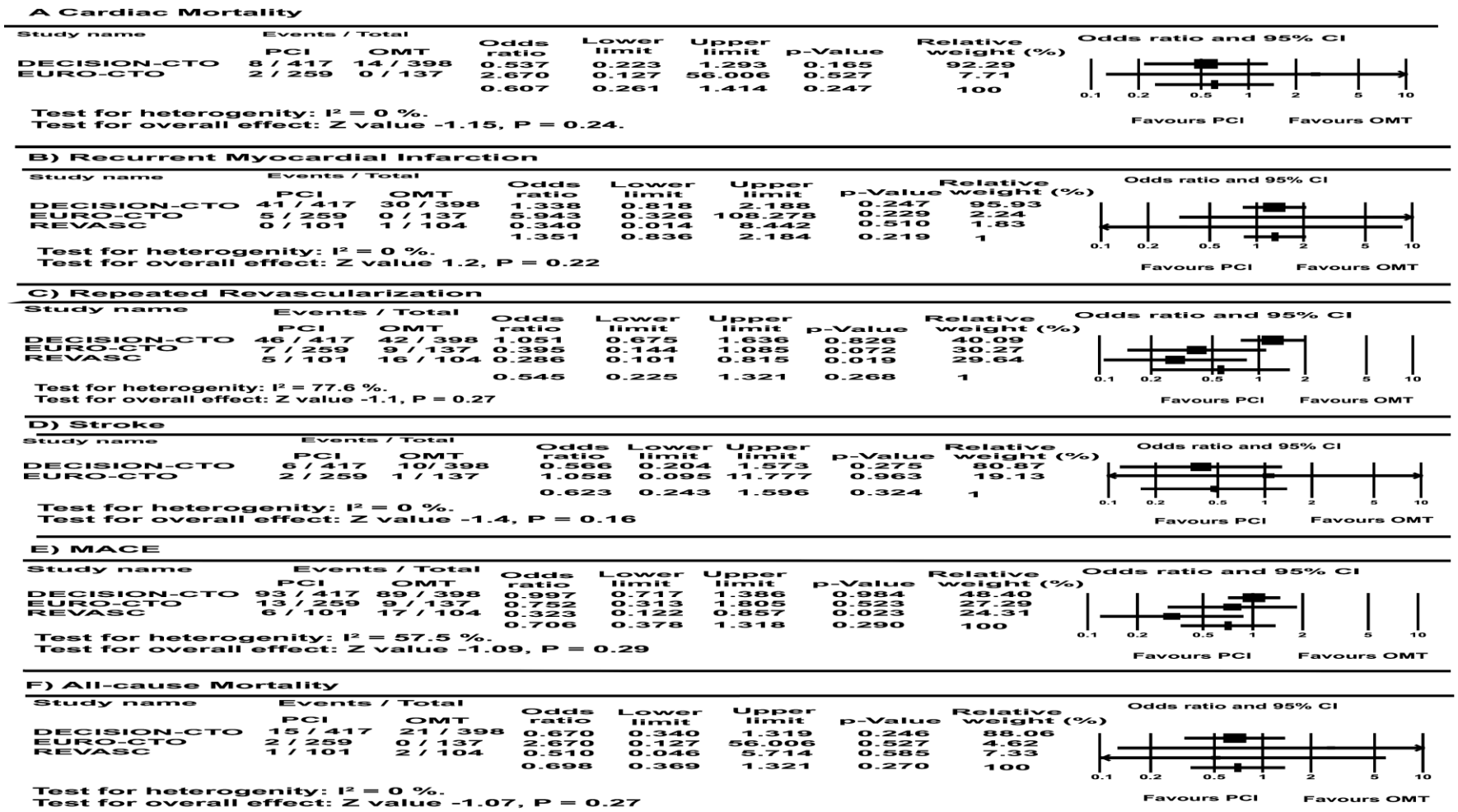
Supplemental Figure 2. Forest plot of major adverse cardiac events (MACE) and all-cause mortality. There was no significant difference between percutaneous coronary intervention (PCI) and optimal medical therapy regarding MACE (odds ratio [OR] 0.76; 95% confidence interval [CI] 0.49 – 1.17; p=0.21, I^2 = 73.2%). PCI was associated with reduced all-cause mortality (OR 0.60; 95% CI 0.46 – 0.77; p=0.001, I^2= 0%).



Supplemental Figure 3. Forest plot of major adverse cardiac events (MACE), excluding the Italian registry study that had a heterogeneous definition for MACE (odds ratio [OR] 0.86; 95% confidence interval [CI] 0.55 – 1.34; p=0.52).



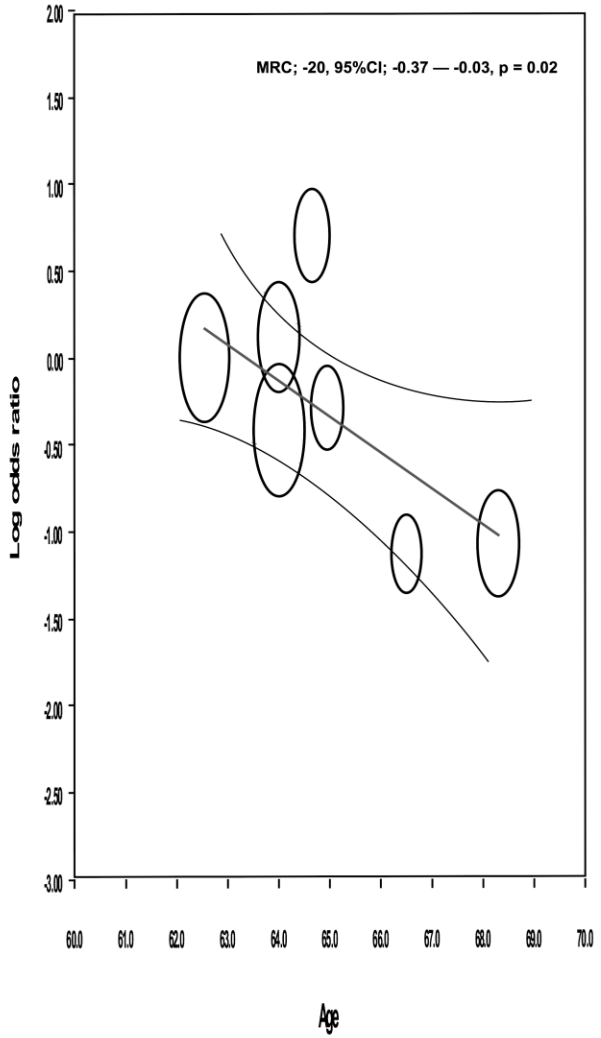
Supplemental Figure 4. Forest plots of sensitivity analysis using "one-study removal approach" of cardiac mortality, recurrent myocardial infarction, repeated revascularization, all-cause mortality and major adverse cardiac events (MACE).



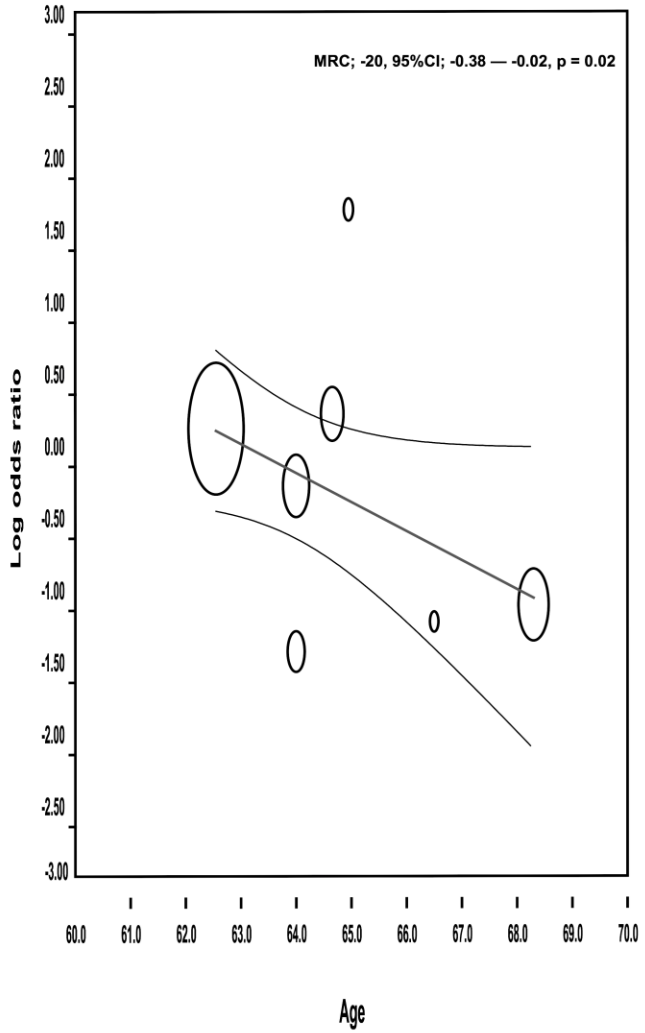
Supplemental Figure 5. Forest plots of subgroup analysis focused on the included randomized controlled trials in our meta-analysis showing cardiac mortality, recurrent myocardial infarction (MI), repeated revascularization, stroke, major adverse cardiac events

(MACE) and all-cause mortality outcomes. There was no significant difference between percutaneous coronary intervention and optimal medical therapy in terms of cardiac mortality (OR 0.60; 95% CI 0.26 – 1.41, p=0.24, I^2 = 0%), recurrent MI (OR 1.35; 95% CI 0.83 – 2.18, p=0.21, I^2 = 0%), repeated revascularization (OR 0.54; 95% CI 0.22 – 1.32, p=0.26, I^2 = 77.6%), stroke (OR 0.62; 95% CI 0.24– 1.59, p=0.32, I^2 = 0%), MACE (OR 0.70; 95% CI 0.37 – 1.31, p=0.29, I^2 = 57.5%) and all-cause mortality (odds ratio [OR] 0.69; 95% confidence interval [CI] 0.36 – 1.32, p=0.27, I^2 = 0%).

A) Regression of Log odds ratio of MACE on Age



B) Regression of Log odds ratio of recurrent myocardial infarction on Age



Supplemental Figure 6. Meta-regression analysis of the log odds ratio (OR) of major adverse cardiac events (MACE) and recurrent myocardial infarction (MI) plotted against age. Meta-regression analysis showed a significant interaction between the log OR MACE (meta-regression coefficient (MRC); -0.20, 95% confidence interval [CI]; -0.37— - 0.03; p= 0.02) and recurrent MI (MRC; -0.20, 95% CI; -0.38 — 0.02; p= 0.02).