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Staged Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With ST-Segment–Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis

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***Background*—**Studies have shown that chronic total occlusion (CTO) in a noninfarct-related artery in patients with ST-segment–elevation myocardial infarction is linked to increased mortality. It remains unclear whether staged revascularization of a noninfarct-related artery CTO in patients with ST-segment–elevation myocardial infarction translates to improved outcomes. We performed a meta-analysis to compare outcomes between patients presenting with ST-segment–elevation myocardial infarction with concurrent CTO who underwent percutaneous coronary intervention of noninfarct-related artery CTO versus those who did not.

***Method and Results*—**We conducted an electronic database search of all published data. The primary end point was major adverse cardiovascular events. Secondary end points were all-cause mortality, cardiovascular mortality, myocardial infarction, repeat revascularization with either percutaneous coronary intervention or coronary artery bypass grafting, stroke, and heart failure readmission. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed. Random effects model was used and heterogeneity was considered if I^2 >25. Six studies (n=1253 patients) were included in the analysis. There was a significant difference in major adverse cardiovascular events (OR, 0.54; 95% CI, 0.32–0.91), cardiovascular mortality (OR, 0.43; 95% CI, 0.20–0.95), and heart failure readmissions (OR, 0.57; 95% CI, 0.36–0.89), favoring the patients in the CTO percutaneous coronary intervention group. No significant differences were observed between the 2 groups for all-cause mortality (OR, 0.47; 95% CI, 0.22–1.00), myocardial infarction (OR, 0.78; 95% CI, 0.41–1.46), repeat revascularization (OR, 1.13; 95% CI, 0.56–2.27), and stroke (OR, 0.51; 95% CI, 0.20–1.33).

***Conclusions*—**In this meta-analysis, CTO percutaneous coronary intervention of the noninfarct-related artery in patients presenting with ST-segment–elevation myocardial infarction was associated with a significant reduction in major adverse cardiovascular events, cardiovascular mortality, and heart failure readmissions. **(*J Am Heart Assoc*. 2018;7:e008415. DOI: 10.1161/JAHA.117.008415.)**

Key Words: chronic total occlusion • meta-analysis • percutaneous coronary intervention • ST-segment–elevation myocardial infarction

Acute ST-segment–elevation myocardial infarction (STEMI) is typically caused by thrombotic occlusion of a coronary artery. The treatment of choice for STEMI is percutaneous coronary intervention (PCI) to restore blood flow to the occluded infarct-related artery.[1,2] Approximately 50% of patients presenting with STEMI are found to have multivessel coronary artery disease (CAD) with concomitant stenotic lesions in noninfarct-related arteries (nIRAs) and

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Accompanying Tables S1 through S3 and Figures S1 through S6 are available at http://jaha.ahajournals.org/content/7/8/e008415/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Our findings suggest that routine staged percutaneous coronary intervention (PCI) of a concurrent chronic total occlusion in a noninfarct-related artery after successful primary PCI in patients with ST-segment–elevation myocardial infarction is feasible and safe.
- Staged PCI of a concurrent chronic total occlusion is associated with reduction in mortality, major adverse cardiovascular events, and heart failure readmissions without increased risk of stroke and myocardial infarction.

What Are the Clinical Implications?

- When clinicians decide the treatment strategy after primary PCI of the culprit artery in patients with ST-segment–elevation myocardial infarction with concurrent chronic total occlusion in a noninfarct-related artery, our results suggest that staged PCI of the chronic occlusion is a more appropriate treatment strategy.
- Further larger randomized controlled trials are needed to fully understand the role of chronic total occlusion revascularization in patients with ST-segment–elevation myocardial infarction.

≈12% to 13% are found to have a chronic total occlusion (CTO) in an nIRA.[3,4] Prior studies have shown that the presence of a CTO in an nIRA in patients with STEMI is linked to an increase in short- and long-term mortality.[4,5] Moreover, it has been suggested that the presence of a CTO is associated with worse outcomes compared with the presence of multivessel CAD without a CTO.[3,5,6] Although there is evidence that multivessel revascularization in patients with STEMI might be beneficial,[7] it remains unclear whether revascularization via PCI of an nIRA CTO, and in particular in patients with STEMI, is translated to improved outcomes. The current literature includes several small studies which suggest that successful revascularization of CTO lesions is associated with a lower risk of death, stroke, and coronary artery bypass grafting; less recurrent angina; and improvement of left ventricular ejection fraction (LVEF).[8,9] However, a recent randomized prospective trial did not find benefit for patients with STEMI who had PCI of an nIRA CTO.[10] We therefore performed a meta-analysis to compare outcomes between patients presenting with STEMI who underwent PCI revascularization of nIRA CTO versus those who did not.

Methods

The authors declare that all supporting data are available within the article and its online supplementary material.

A protocol for this systematic review was created, which we posted online and registered in PROSPERO (CRD42017065380). We followed the guidelines outlined by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[11]

Search Strategy

We conducted a literature search of PubMed Central, Embase, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Google Scholar databases and the scientific session abstracts in *Circulation*, the *Journal of the American College of Cardiology*, and the *European Heart Journal*. Oral presentations at scientific sessions were included using the respective websites: Transcatheter Cardiovascular Therapeutics (www.tctmd.com), EuroPCR (www.europcr.com), American College of Cardiology (www.acc.org), American Heart Association (www.heart.org), and European Society of Cardiology (www.escardio.org). Moreover, we performed manual searches of reference lists that included studies, reviews, editorials, and letters, as well as related conference proceedings. Last accessed as up to date: December 30, 2017.

Search term keywords were: "randomized controlled trial," "nonrandomized studies," "myocardial infarction," "ST-segment–elevation myocardial infarction," "acute coronary syndromes," "multivessel," "chronic total occlusion," "nonculprit," "staged," "percutaneous coronary intervention," and "revascularization," as well as various combinations of these terms. No language restriction was implemented. Only adult human studies were included.

Inclusion Criteria

Studies that fulfilled the following specifications were included: (1) randomized controlled trials (RCTs) or nonrandomized studies of patients who presented with acute STEMI and were found to have concurrent CTO in an nIRA during the primary PCI for STEMI; and (2) direct comparison provided between patients with successful revascularization of CTO lesions in the nIRA and patients with failed or nonattempted revascularization (non-PCI group) of CTO lesions in the nIRA. If data were not provided as treated, the outcomes were analyzed as intention to treat.

Exclusion criteria were pregnancy; age younger than 18 years; diagnoses of non-STEMI, unstable angina, or chronic ischemic heart disease; and/or not meeting the above-mentioned inclusion criteria.

Two reviewers (W.O. and P.V.) independently searched the studies and collected data. Data were extracted using standardized protocol and reporting forms. Disagreements were resolved by consensus or, if necessary, by a third party (M.W. and D.M.). Two reviewers (P.V. and D.B.) independently

assessed the risk of bias of RCTs using standard criteria defined in the *Cochrane Handbook for Systematic Reviews of Interventions*[12] and the Newcastle-Ottawa Scale for nonrandom controlled studies.[13]

Study End Points

The primary end point was the incidence of major adverse cardiovascular events (MACE). Secondary end points were all-cause mortality, cardiovascular mortality, new myocardial infarction (MI), repeat revascularization (RRV) either with PCI or coronary artery bypass grafting, stroke, and heart failure (HF) readmission. Trial-specific definitions were also used for individual end points.

Statistical Analysis

The collected data were summarized across treatment arms using the odds ratio (OR) random effect models along with a stratified Fisher exact test. We evaluated heterogeneity of effects using the I^2 statistic (defined as I^2 >25%). To address publication bias, we used 4 methods: funnel plots, Begg-Mazumdar test, Egger test, and the Duval and Tweedie test. Meta-regression analyses were performed to determine whether the effects of mortality were modulated by prespecified study-level factors including age, male sex, diabetes mellitus (DM), hypertension, hyperlipidemia, smoking, LVEF, 3-vessel CAD, and CTO of the left anterior descending artery (LAD). All variables except for age were represented as proportions in the studies. Meta-regression was performed with unrestricted maximum-likelihood method (inverse variance-weighted regression) on the OR log-transformed before being used as independent variables in linear meta-regression analyses. Sensitivity analyses were performed using the leave-one-study-out method in order to address the influence of each study by testing whether deleting each individually would significantly change the pooled results of the meta-analysis. Additionally, chronological cumulative analyses were used to test whether the effect size and precision would shift based on technical advancement of stents, CTO equipment, antithrombotic therapy, and CTO strategies. Finally, we performed Mantel–Haenszel fixed effect model analysis to test whether the overall effects change with this statistical analysis. The statistical analysis was performed using Comprehensive Meta-Analysis Software version 2.0 (Biostat, Inc).

Study Selection and Characteristics

The search strategy identified a total of 527 potential articles (Figure 1). After removing duplicates and articles that did not meet inclusion criteria, we screened 94 titles and abstracts. Of these, 16 were selected for further review. Ultimately, 5 observational studies and 1 RCT satisfied all inclusion criteria.[10,14–18] All selected studies were published in journals as full English articles. Overall, the studies enrolled a total of 1253 patients. Among this population, 692 patients underwent successful revascularization of CTO lesions in the nIRA (PCI group) and 561 patients failed revascularization of CTO lesions in the nIRA or revascularization was not attempted. The follow-up ranged from in-hospital discharge to up to 5 years. Patients in the PCI group were slightly younger (mean age 64 years) compared with patients in the non-PCI group (mean age 66 years). At the time of STEMI presentation, patients in the PCI group were more likely to have the culprit lesion in the LAD as compared with patients in the non-PCI group (38.8% versus 33.6%), and were more likely to have multivessel disease (51.3% versus 48%, respectively). The CTO lesions were staged up to 30 days after primary PCI. The average ejection fraction between the 2 groups differed by only 1.2% in favor of the PCI group. Study characteristics are shown in Tables 1 and 2, and inclusion and exclusion criteria of the selected studies are shown in Table S1.

Quantitative Data Synthesis

Efficacy Outcomes

Major adverse cardiovascular events

A total of 199 MACE were reported: 17.6% (98/556) in the PCI group and 24.8% (101/407) in the non-PCI group. Overall, there was a significant difference in MACE favoring patients in the PCI group over patients in the non-PCI group (OR, 0.54; 95% confidence interval [CI], 0.32–0.91 [*P*=0.02]) (Figure 2). Stratified Fisher exact test analysis was also significant, favoring the PCI group (OR, 0.64; 95% CI, 0.47–0.88 [*P*=0.008]).

All-cause mortality

A total of 125 all-cause mortality events were reported: 7.6% (53/692) in the PCI group and 12.8% (72/561) in the non-PCI group. Overall, there was no significant difference in all-cause mortality between the groups (OR, 0.47; 95% CI, 0.22–1.00 [*P*=0.05]) (Figure 2). Stratified Fisher exact test analysis was significant, favoring the PCI group (OR, 0.56; 95% CI, 0.38–0.81 [*P*=0.003]).

Cardiovascular mortality

A total of 79 cardiovascular mortality events were reported: 6.5% (45/692) in the PCI group and 11.7% (66/561) in the non-PCI group. Overall, there was a significant difference favoring patients in the PCI group over patients in the non-PCI group (OR, 0.43; 95% CI, 0.20–0.95 [*P*=0.04]) (Figure 2). Stratified Fisher exact test analysis was also significant,

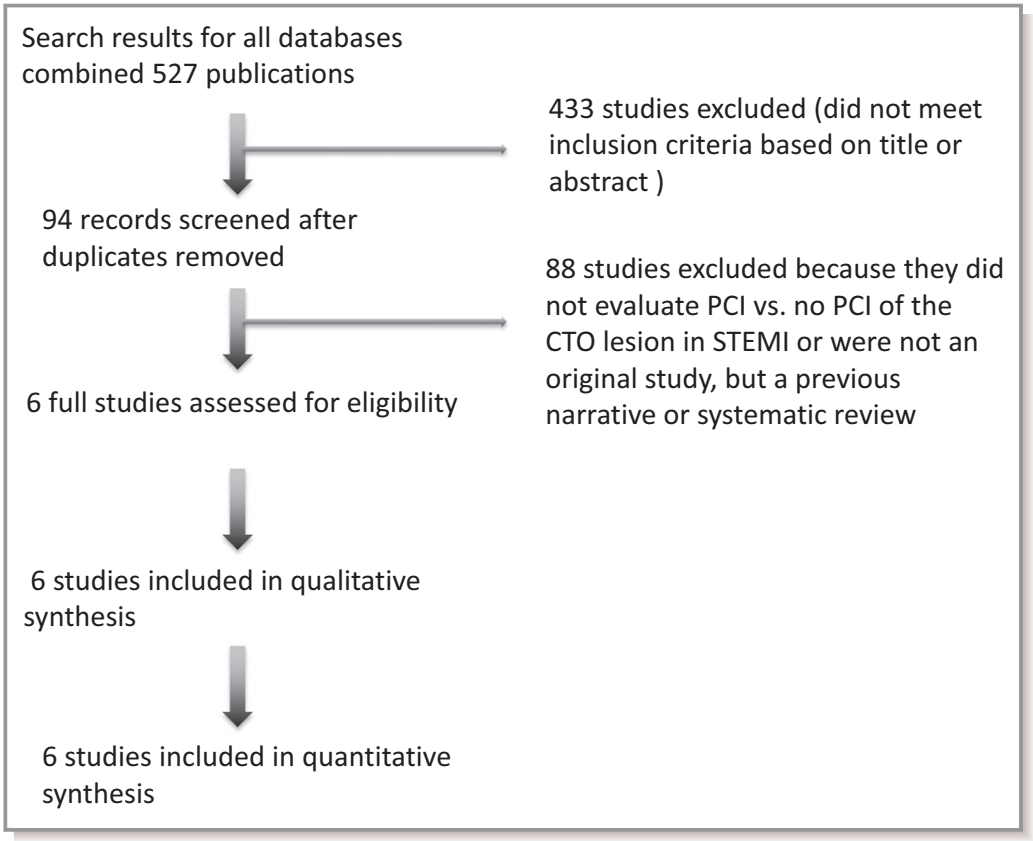

Figure 1. Flow chart of the literature review. From 527 studies identified from the initial search, a total of 6 studies were included after screening titles and reviewing the full articles of potentially relevant studies. CTO indicates chronic total occlusion; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

favoring the PCI group (OR, 0.52; 95% CI, 0.35–0.77 [*P*=0.001]).

New Myocardial Infarction

A total of 34 new MI cases were reported: 3.3% (23/692) in the PCI group and 3.3% (19/561) in the non-PCI group. Overall, there was no significant difference between the groups (OR, 0.78; 95% CI, 0.41–1.46 [*P*=0.43]) (Figure 3). Stratified Fisher exact test analysis was also not significant between groups (OR, 0.98; 95% CI, 0.52–1.82 [*P*=0.98]).

Repeat revascularization

A total of 202 RRVs were reported: 20.9% (145/692) in the PCI group and 17.8% (100/561) in the non-PCI group. Overall, there was no significant difference between the groups (OR, 1.13; 95% CI, 0.56–2.27 [*P*=0.74]) (Figure 3). Stratified Fisher exact test analysis was also not significant between groups (OR, 1.22; 95% CI, 0.92–1.62 [*P*=0.18]).

Stroke

A total of 20 strokes were reported: 2.1% (8/384) in the PCI group and 3.4% (12/356) in the non-PCI group. Overall, there was no significant difference between the groups (OR, 0.51; 95% CI, 0.20–1.33 [*P*=0.17]) (Figure 3). Stratified Fisher exact test analysis was also not significant between groups (OR, 0.60; 95% CI, 0.24–1.51 [*P*=0.39]).

Heart Failure Readmission

A total of 50 hospitalizations from HF were reported: 9.8% (45/486) in the PCI group and 17.1% (44/296) in the non-PCI group. Overall, there was a significant difference in HF readmissions favoring patients in the PCI group over patients in the non-PCI group (OR, 0.57; 95% CI, 0.36–0.89 [*P*=0.01]) (Figure 3). Stratified Fisher exact test analysis was also significant, favoring the PCI group (OR, 0.58; 95% CI, 0.37–0.91 [*P*=0.02]).

Sensitivity Analysis

Sensitivity analysis involving the removal of each of the studies sequentially demonstrated that if some of the studies were removed from the analysis, they influenced the summary risk estimates for cardiovascular MACE, cardiovascular mortality, and HF, making the overall results nonsignificant (Figure S1). MACE, cardiovascular, and HF readmission changed significantly ($P<0.05$) in the overall final effect in the chronologic cumulative analysis for each outcome before

Table 1. Design and Outcomes of the Studies Included in the Meta-Analysis

Author/Year	Design	Total Patients, No.	Follow-Up	Primary Outcomes	MACE Definition
Yang 2011[14]	Single center, retrospective	136	2 y	Cardiac mortality and occurrence of MACE	Cardiac death, recurrent myocardial infarction, repeat revascularization (PCI and/or CABG), and heart failure rehospitalization
Shi 2014[15]	Single center, retrospective	148	3 y	Survival and occurrence of MACE	Cardiac death, recurrent myocardial infarction, repeat revascularization (PCI and/or CABG), and rehospitalization because of heart failure
Valenti 2014[16]	Multicenter registry, retrospective	169	1 y	1- and 3-y cardiac survival	Not reported
Watanabe 2016[17]	Multicenter registry, retrospective	121	4 y	All-cause death	Not reported
Deng 2017[18]	Single center, retrospective	377	1 y	Composite of all-cause death, nonfatal myocardial infarction, ischemia-driven coronary revascularization, and hospitalization for heart failure at 1 y	All-cause death, nonfatal myocardial infarction, ischemia-driven coronary revascularization, and hospitalization for heart failure
Henriques 2016[10]	Multicenter RCT	302	4 mo	LVEF and LVEDV, assessed by cardiac MRI at 4 mo	Cardiac death, myocardial infarction, and CABG

CABG indicates coronary artery bypass grafting; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; RCT, randomized controlled trials.

inclusion of all studies in the final effect summary (Figure S2). Sensitivity analysis with a fixed model did not change the significance of the final effect estimates for the analyzed outcomes except for all-cause mortality, which also became significant, favoring PCI of CTO vessels (OR, 0.43; 95% CI, 0.28–0.66) (Figure S3).

Meta-regression

Meta-regression coefficients effects on cardiovascular mortality were not statistically significant for mean age, male sex, DM, hypertension, hyperlipidemia, smoking, LVEF, 3-vessel CAD, or CTO of the LAD (Figure S4).

Bias

Funnel plot did not show asymmetry suggesting bias for all outcomes except for MI (Figure S5). However, after quantifying the observed bias with other methods, there was no evidence of publication bias (Begg-Mazumdar test and Egger test $P>0.05$ for all outcomes explored [Figure S6]). The individual study quality appraisals of the included studies are summarized in Tables S2 and S3.

Discussion

To our knowledge, this is the first meta-analysis assessing the efficacy of successful PCI of an nIRA CTO in patients presenting with STEMI. This meta-analysis has 3 main findings. First, there is a reduction in the composite end point of MACE with CTO PCI of the nIRA in patients with STEMI after primary PCI. Second, we demonstrated a reduction in cardiovascular mortality and HF readmission when PCI is implemented successfully in CTO nIRA as compared with the failed/nonattempted approach. Last, the risk for stroke, MI, and RRV was not remarkably different between the successful CTO-PCI group and the non-PCI group. Although all-cause mortality did not significantly differ between groups, this discrepancy could be explained by the noncardiovascular mortality observed in the non-PCI group, while cardiovascular mortality favored the CTO PCI group. As a result, all-cause mortality was unchanged in the 2 study groups. Unfortunately, noncardiovascular death can be influenced by cardiovascular disease as well as many other comorbidities, and determination of causes of death can be difficult, particularly in patients with multiple organ dysfunction. Therefore, interpretation of all-cause mortality in such patients is controversial.

In their meta-analysis, O'Connor et al[19] demonstrated that the presence of coronary CTO in the nIRA in patients presenting with STEMI is associated with increased short- and long-term all-cause mortality. The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Intervention guidelines for PCI suggest that CTO PCI is reasonable when

Table 2. Baseline Clinical and Demographic Characteristics of the Studies Included in the Meta-Analysis

Author/Year		Age, y	Male, %	Hypertension, %	DM, %	Hyperlipidemia, %	Smoking, %	Prior MI, %	3 Vessel, %	EF, %	CTO LAD%	CTO LCx	CTO RCA	Staged CTO After Primary PCI
Yang 2011[14]	PCI	66	82	70	36	20	39	26	68	46	38	33	36	7 to 10 d
	Non PCI	69	82	76	37	22	37	33	65	47	37	39	29	
Shi 2014[15]	PCI	N/A	78	65	23	55	45	28	51	N/A	36	30	34	7 to 10 d
	Non PCI	N/A	83	69	23	58	40	33	48	N/A	42	29	29	
Valenti 2014[16]	PCI	64	85	55	17	36	50	19	59	36	33	33	34	Up to 30 d
	Non PCI	69	73	67	15	41	30	29	48	38	17	29	55	
Watanabe 2016[17]	PCI	66	84	73	37	N/A	42	10	N/A	48	31	36	33	4 to 17 d
	Non PCI	67	79	84	23	N/A	47	19	N/A	49	27	44	29	
Deng 2017[18]	PCI	65	79	78	33	80	58	32	33	49	31	33	36	7 to 28 d
	Non PCI	68	79	74	28	73	52	35	33	50	39	29	32	
Henriques 2016[10]	PCI	60	89	40	15	35	52	13	42	41	24	32	43	Within 7 d
	Non PCI	60	82	45	16	34	49	16	44	42	35	24	51	

CTO indicates chronic total occlusion; DM, diabetes mellitus; EF, ejection fraction; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; N/A, not available; PCI, percutaneous coronary interventions; RCA, right coronary artery.

performed by operators with appropriate expertise (class IIa, level B).[20] Although the association between CTO and worse outcomes has been well-established, it is unknown whether revascularization of the nIRA CTO in patients with STEMI is actually translated into improved outcomes. Our study further extends these conclusions to patients with STEMI who underwent PCI in nIRA CTO as shown in another meta-analysis of contemporary RCTs in patients with STEMI with multivessel CAD.[7] The idea that patients with acute STEMI and concurrent nIRA CTO would demonstrate clinical benefit from CTO PCI was generated from the apparent 2-fold increased mortality and morbidity rates among patients with STEMI and multivessel CAD and CTO.[4,5,21] Even among patients without STEMI, increased mortality has been attributed to the presence of CTOs in nIRAs.[3,6] One of the possible mechanisms of increased mortality in patients with CTO could be a larger infarct size caused by the acute occlusion of a donor artery to CTO. The decreased flow of the donor artery might result in myocardial injury and necrosis in the myocardial area in which the myocardial perfusion was dependent on the collateral flow from the infarct-related artery. It has also been reported that the presence of multivessel CAD is associated with adverse outcomes compared with single-vessel CAD in patients with STEMI, mainly attributed to the increased mortality caused by HF.[22] The presence of a CTO was associated with reduced residual LVEF and with further deterioration of LVEF during follow-up.[3] It is challenging to discern whether CTO in an nIRA is only a result of multiple cardiovascular comorbidities or whether it exacerbates mortality in patients with STEMI, but it might potentially be a modifiable factor in the improvement of mortality. The meta-regression performed in our analysis of successful CTO PCI did not show an association between cardiovascular mortality and known cardiovascular risk factors for adverse outcomes in patients with STEMI.

Contemporary research from George et al[23] also demonstrated a mortality benefit for CTO revascularization in a registry investigation of >13 000 patients in the United Kingdom. Possible explanations for the underlying mechanism of the clinical benefit of opening CTO lesions include the improvement in blood flow in the peri-infarct area and recovery of contractile function of the hibernated areas perfused by in the CTO territory. Other possible mechanisms include an increase in electrical stability with the associated reduction of fatal arrhythmia, and an increased tolerance to further coronary ischemic events. The overall benefit of a successful PCI could be translated to improvement of LVEF, avoiding left ventricular remodeling, and subsequent worsening LVEF and development of HF.

The results of our analysis do not mirror those of the only RCT to evaluate this topic. The EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment–Elevation Myocardial Infarction) trial randomized patients presenting with acute STEMI and concurrent CTO in an nIRA to receive either early revascularization (within 1 week) or conservative (non-PCI) therapy.[10] They reported a relatively high level of successful CTO PCI (77%). However, there was no significant improvement in cardiac deaths, recurrent MI, MACE, or LVEF. The recently reported findings of the DECISION-CTO (Optimal

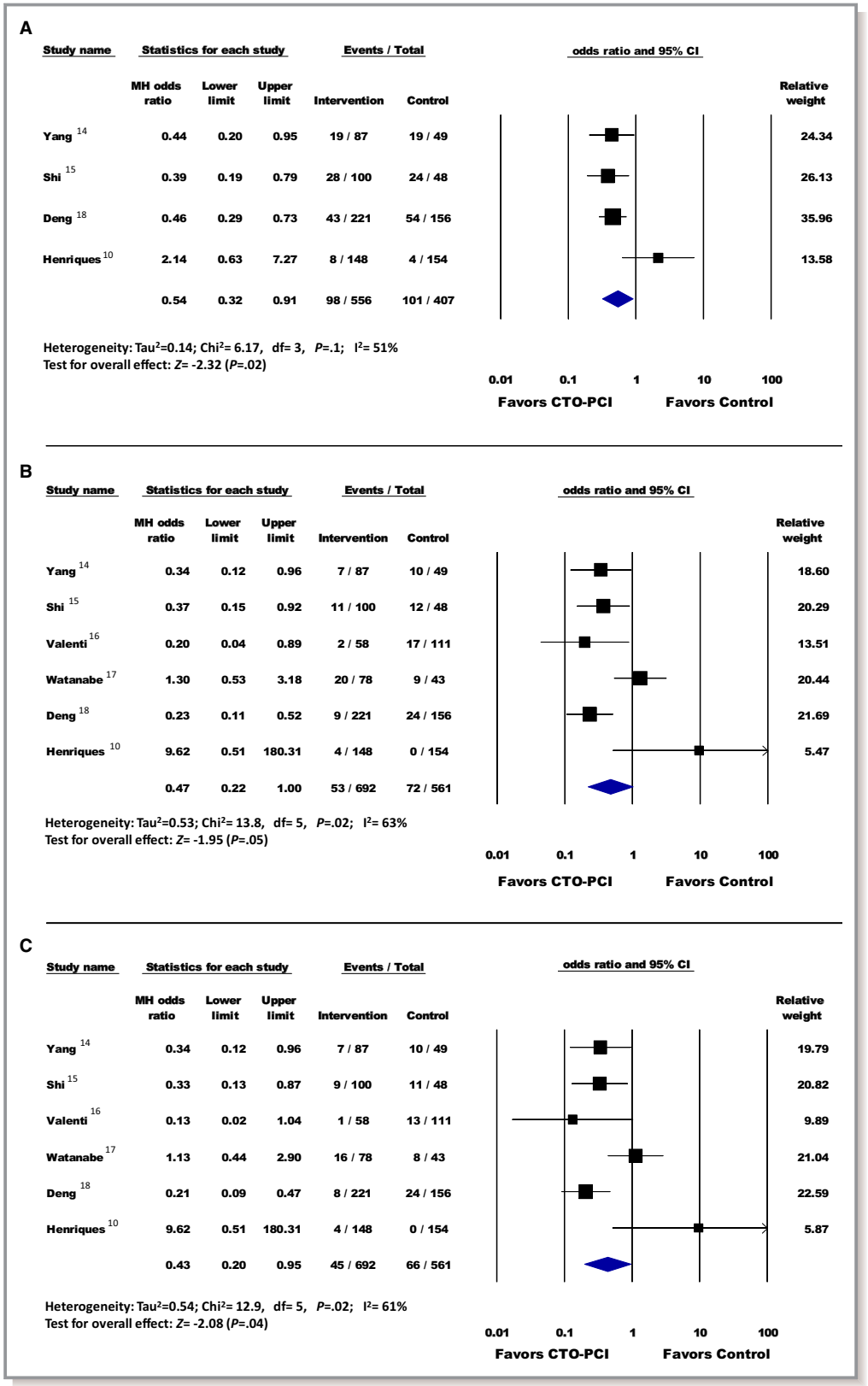

Figure 2. A, Major adverse cardiovascular events; (B) all-cause mortality; (C) cardiovascular mortality. Forest plot reporting the odds ratios in patients with ST-segment–elevation myocardial infarction (STEMI) with percutaneous coronary intervention (PCI) of the chronic total occlusion (CTO) lesion vs no PCI of CTO lesion. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% confidence interval [CI]); width of the shaded square represents the size of the population).

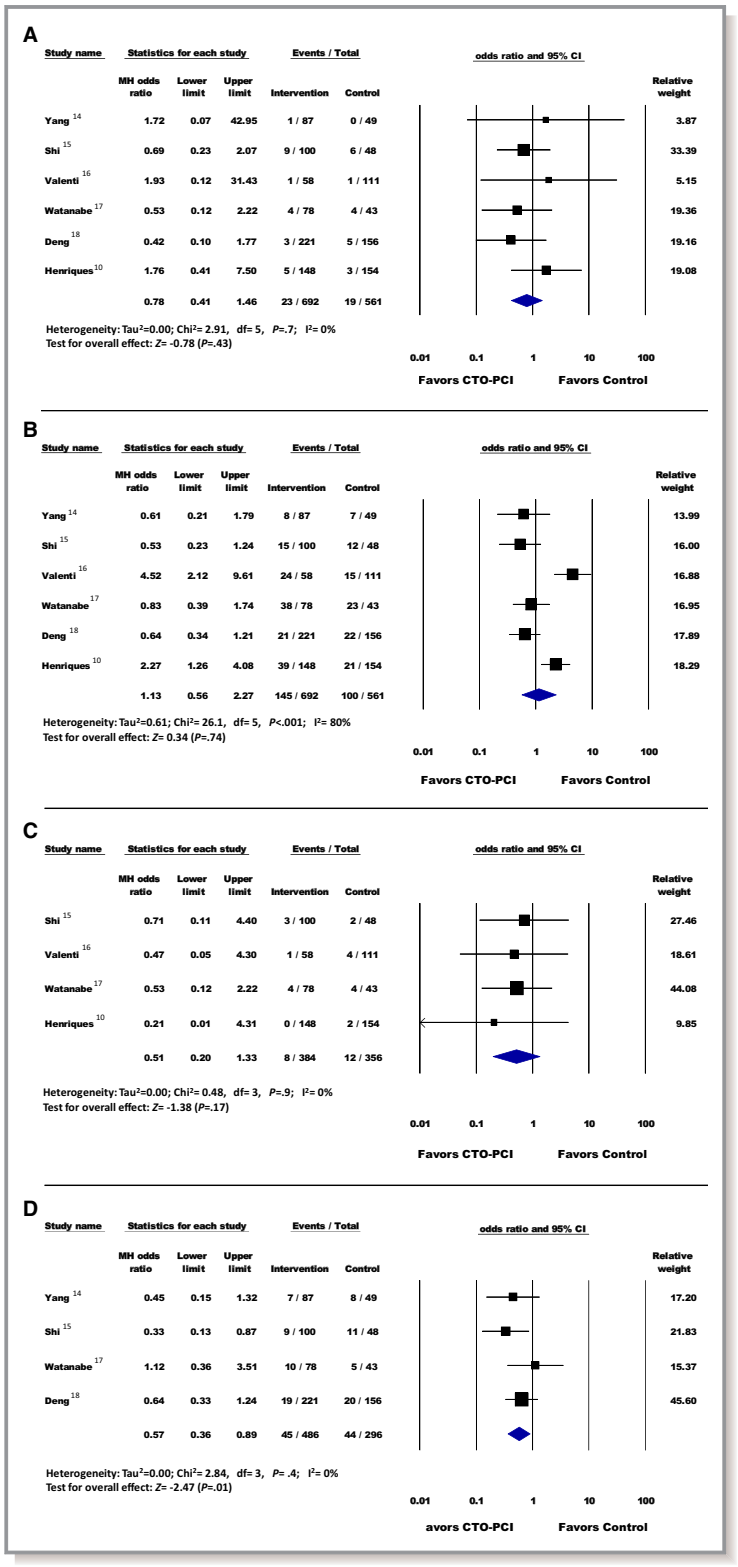

Figure 3. A, Myocardial infarction; (B) repeat revascularization; (C) stroke; (D) heart failure readmission. Forest plot reporting the odds ratios in patients with ST-segment–elevation myocardial infarction (STEMI) with percutaneous coronary intervention (PCI) of the chronic total occlusion (CTO) lesion vs no PCI of CTO lesion. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% confidence interval [CI]); width of the shaded square, size of the population).

Medical Therapy With or Without Stenting For Coronary Chronic Total Occlusion) trial by Park et al[24] call into question the value of CTO PCI in general. The DECISION-CTO study evaluated outcomes in patients without ACS who underwent revascularization of CTO. They demonstrated that optimal medical therapy was noninferior to CTO PCI in 834 patients randomized to each arm. However, they excluded patients with LVEF <30%—a group of patients who may derive the most benefit from CTO PCI. Of note, this trial was stopped early secondary to slow enrollment. EuroCTO (Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) showed a high procedural success rate of CTO PCI with an overall low procedural risk. Also, there was an improvement in clinical symptoms in patients treated with PCI compared with optimal medical therapy based on the Seattle Angina Questionnaire, subscales of physical limitation, and angina frequency. The PCI group also showed a trend towards improved quality of life and significantly greater absolute freedom from angina.[25]

Our meta-analysis did not demonstrate significant benefit with respect to stroke, new MI, and RRV among patients who underwent successful CTO PCI. Possible hypotheses to explain the absence of clinical benefit in revascularization of these lesions could be that myocardial injury resulting from the presence of CTOs is long-standing, reducing the chance for viability, and that remodeling has likely already occurred, thus, minimizing the benefit from reperfusion. A number of factors should be considered when selecting patients for CTO-PCI, including not only the presence of symptoms and extent of ischemia but also the degree of myocardial viability. Using cardiovascular magnetic resonance imaging (MRI), a subgroup analysis of the EXPLORE trial showed that benefit of CTO PCI in dysfunctional but viable segments of myocardium, as compared with nonviable myocardium where no improvement was observed after CTO PCI compared with no CTO PCI.[26] Further research is needed to evaluate the use of viability in patients with STEMI with nonculprit CTO lesions and the effect of PCI on clinical outcome.

The way of dealing with nIRA lesions in patients with STEMI remains a target of controversy because of a paucity of randomized data and conflicting results in several observational studies. CTO is the most complex and challenging coronary lesion for PCI. There is a need for accurate risk stratification in patients who potentially might benefit from PCI of nIRA CTOs lesions. Despite the progress in CTO interventions, certain complications still persist. Procedure-related mortality and MI have been reported as 1% and 5%, respectively, despite the evolution of PCI techniques and equipment, and adjunctive pharmacological therapy.[27] The preparation and experience of the operators having a thorough understanding of potential complications and the availability of dedicated equipment to treat these complications will improve the rate of successful revascularization and minimize the risks.

Limitations

Our meta-analysis has several limitations. First, this is a meta-analysis of RCTs and observational study data. Potential biases are likely to be greater for observational studies compared with RCTs; therefore, results should always be interpreted with caution when they are included in reviews and meta-analyses. The presence of treatment selection bias is a major criticism against most observational studies, and may threaten the validity of study results when the sickest patients are more likely to receive one treatment strategy over another. In the absence of prospective allocation of patients to treatment strategies, there is an inherent bias that favors survival in those who live beyond the initial treatment to undergo staged treatment. The inherent bias and unmeasured confounding elements of observational studies may influence the study results despite multiple sensitivity analyses.[28] Second, this is a meta-analysis performed on study-level data. Third, the definitions, design, treatment exposure, protocols, reporting of adverse outcomes, and risk of enrolled patients differed across studies. These limitations might explain some of the observed heterogeneity for the different outcomes. Fourth, the selection criteria for PCI were diverse between studies. Fifth, crossover treatment was not reported consistently; it might have a significant unrecognized impact on the overall outcomes in nonattempted versus failed PCI. Sixth, in some studies, there was a considerable loss to follow-up, with only a few studies providing detailed outcomes. Therefore, the long-term risks and benefits of CTO PCI are not well-established by these studies. Last, the available PCI equipment and stents used in some of the included studies are not the contemporary technologies available for CTO lesions; therefore, results using the newer-generation technologies might be different from our results. Despite these limitations, the consistency of the magnitude and direction of the overall effect, and the stability of the results after the sensitivity analyses support the robustness of the conclusions and make the overall estimates justified.

Conclusions

In this meta-analysis, CTO PCI of the nIRA in patients presenting with STEMI was associated with a significant reduction of MACE, cardiovascular mortality, and HF readmissions. However, CTO PCI was not associated with a significant improvement in stroke, new MI, and RRV among patients who underwent successful PCI of the CTO lesion.

Further larger RCTs are needed to fully understand the role of CTO revascularization in patients with STEMI.

Disclosures

None.

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Supplemental Material

Table S1. Inclusion and Exclusion Criteria of Studies.

Study	Inclusion Criteria	Exclusion Criteria
Yang et al. [1]	Patients with acute STEMI treated with primary PCI between January 2005 and December 2008, from the Database of Shanghai Rui Jin Hospital Percutaneous Coronary Intervention Outcomes Program. STEMI was diagnosed according to American Heart Association criteria including symptoms consistent with ongoing myocardial ischemia ≥30min, ST-segment elevation ≥1 mm in two contiguous leads or more, new left bundle branch block, or true posterior infarction.	Nine patients were excluded from analysis as they died during hospital stay (n = 6) or were lost to follow-up (n = 3).
Shi et al. [2]	Patients with acute STEMI treated with primary PCI between January 2005 to June 2009 admitted to Guangdong General Hospital. Acute STEMI was diagnosed according to American Heart Association criteria including symptoms consistent with ongoing myocardial ischemia ≥ 30min, accompanied by an electrocardiogram with ST-segment elevation ≥ 1mm(0.1mV) in two contiguous leads or more, new left bundle branch block, or true posterior infarction. Multivessel was defined as ≥ 1 stenosis > 70% of the coronary lumen diameter in > 1 of the noninfarct related epicardial arteries or left main stenosis > 50%. A CTO was defined as a total occlusion in a non-IRA before PCI without antegrade flow or with antegrade or retrograde filling through collateral vessels.	Not available
Valenti et al. [3]	Consecutive patients from the Florence PCI registry treated by successful primary PCI (Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow and residual infarct artery stenosis <30%). Coexisting none infarct-related artery (IRA) CTO. Evidence of viable myocardium in the territory supplied by the CTO vessel.	In-hospital death during the first week after primary PCI.
Watanabe et al. [4]	STEMI patients enrolled in the Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) AMI registry with multi-vessel disease who underwent primary PCI within 24 hours after the symptom. Presence of CTO in the non-IRA	Not available
Deng et al. [5]	STEMI patients who underwent successful primary PCI from January 2006 to December 2014 at The General Hospital of Shenyang Military Region, China and had a non-IRA CTO lesion. CTO was defined as a flow vessel of Thrombolysis in Myocardial Infarction (TIMI) grade 0, and a complete obstruction of a native coronary artery over a period for more than 3 months.	Not available
Henriques et al. [6]	STEMI patients with a non–infarct-related chronic total occlusion undergoing successful primary PCI for STEMI (within 12 hours of onset of symptoms) from November 2007 through April 2015 in 14 centers in Europe and Canada. Successful primary PCI was defined as a residual stenosis of the culprit lesion <30% and the TIMI flow of ≥2. CTO was defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels. CTO located in a coronary vessel with a reference diameter of at least 2.5 mm.	Hemodynamic instability persisting for >48 h after primary PCI and factors precluding reliable CMR imaging such as persistent or permanent atrial fibrillation, severe renal insufficiency, and indications for pacemaker or implantable cardioverter-defibrillator insertion

Table S2. Risk of bias across individual observational studies.

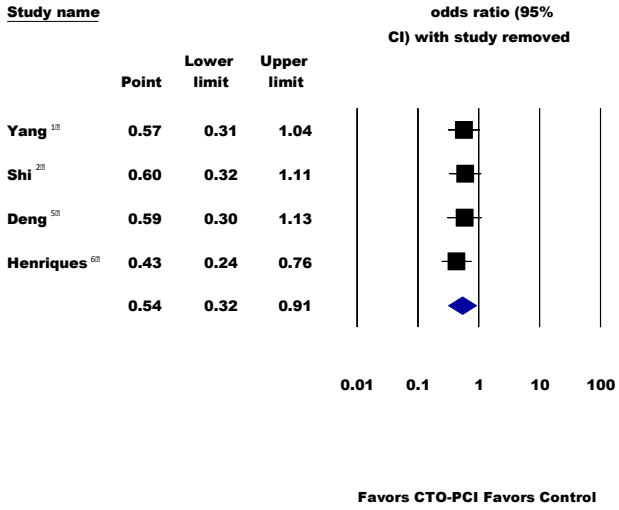
Author	Newcastle-Ottawa Scale
Yang [1]	7/9
Shi [2]	7/9
Valenti [3]	6/9
Watanabe [4]	6/9
Deng [5]	6/9

Table S3. Risk of bias across individual randomized control trials.

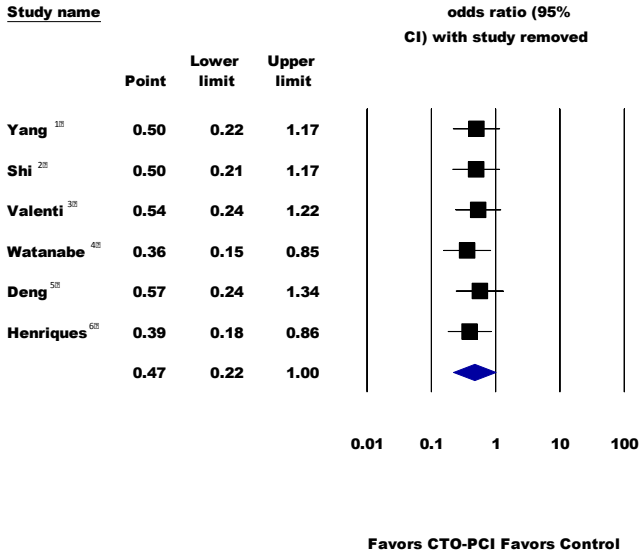
Study Name	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Baseline	Source of funding bias	Academic bias
Henriques [6]	Low	Low	High	Moderate	Low	Low	Low	Low

Figure S1. Sensitivity Analysis with removal of each study one at a time

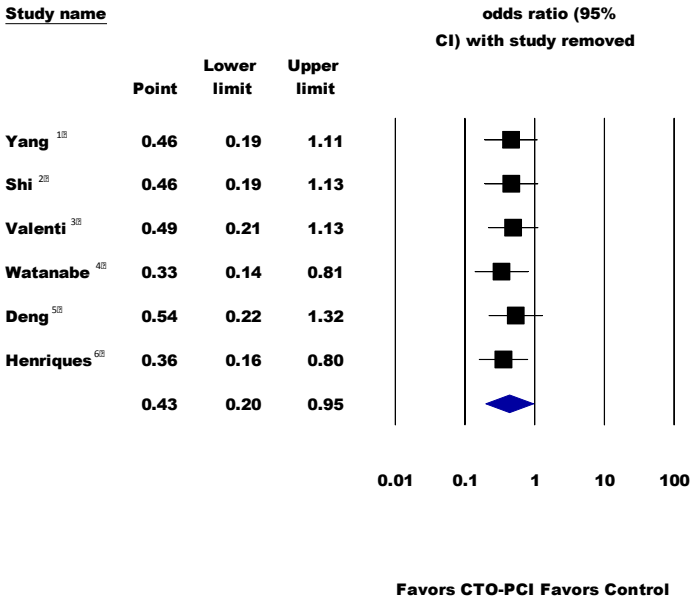
A. Major Adverse Cardiovascular Events



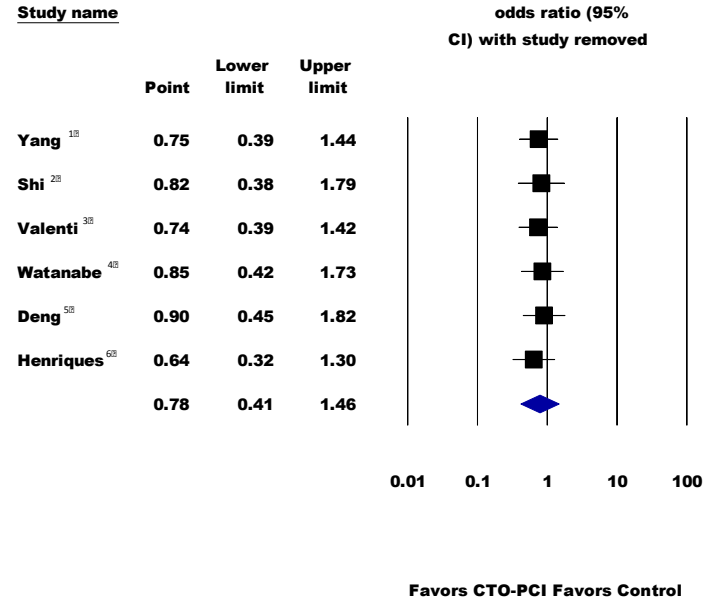
B. All-Cause Mortality



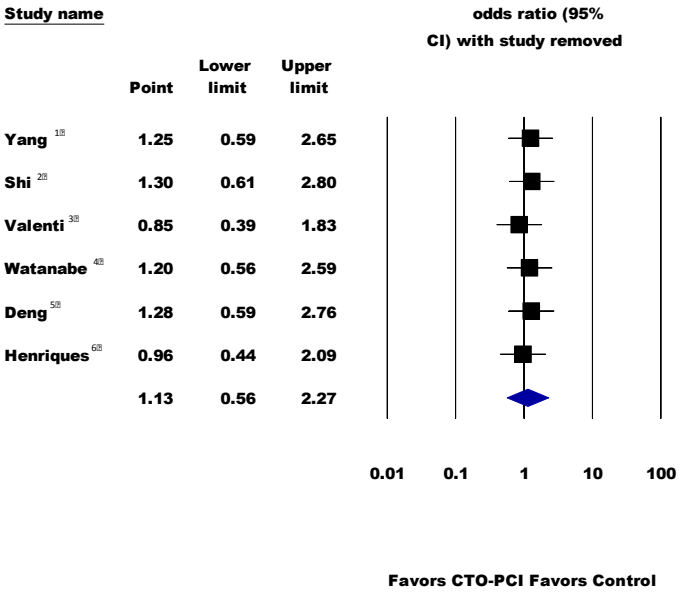
C. Cardiovascular Mortality



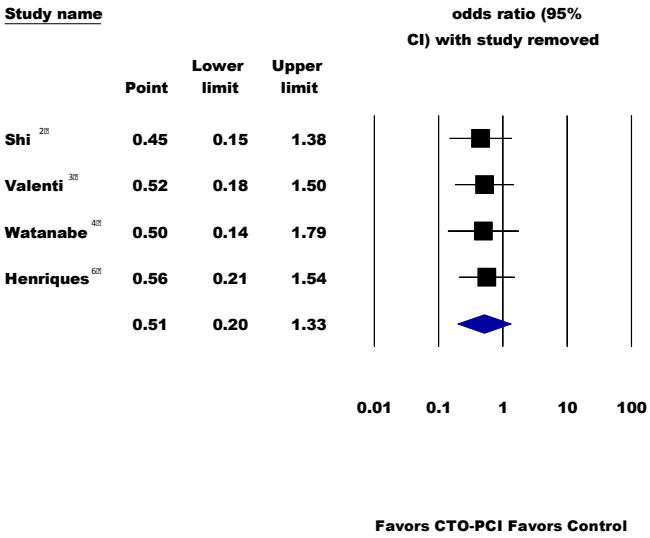
D. Myocardial Infarction



E. Repeat Revascularization



F. Stroke



G. Heart Failure

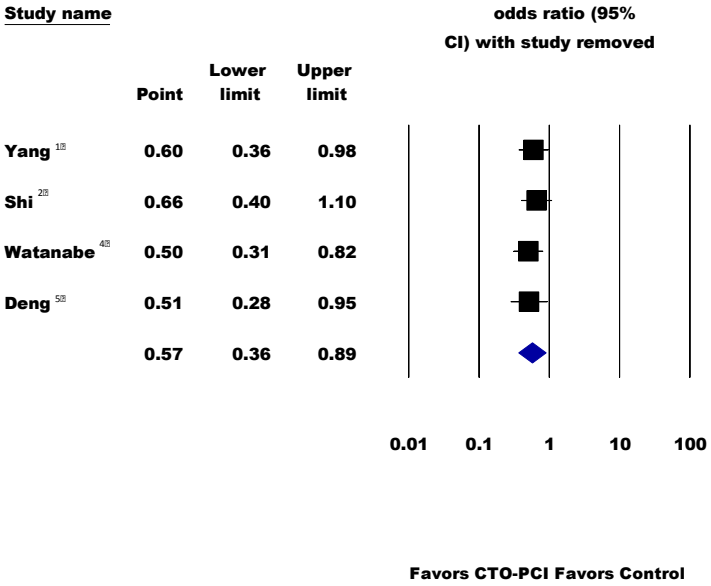
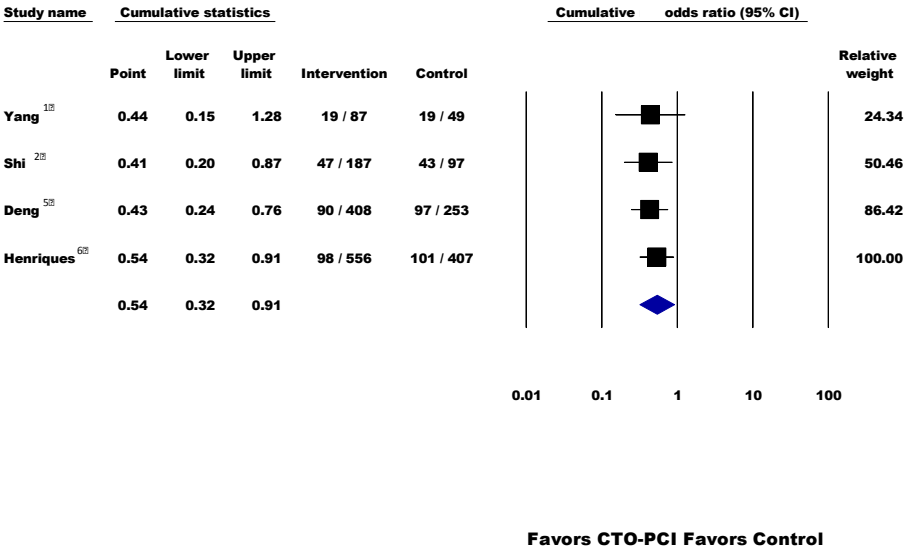
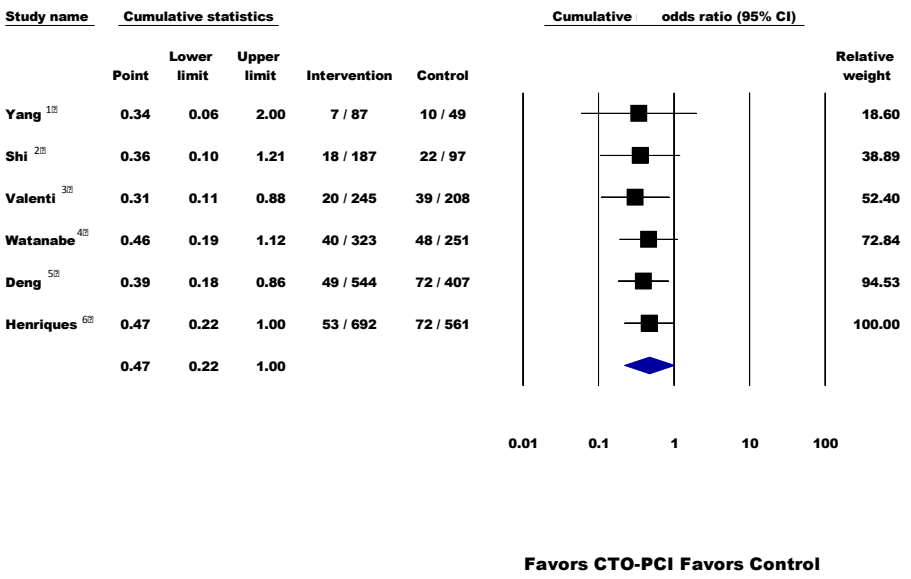


Figure S2. Cumulative analysis for Each Outcome.

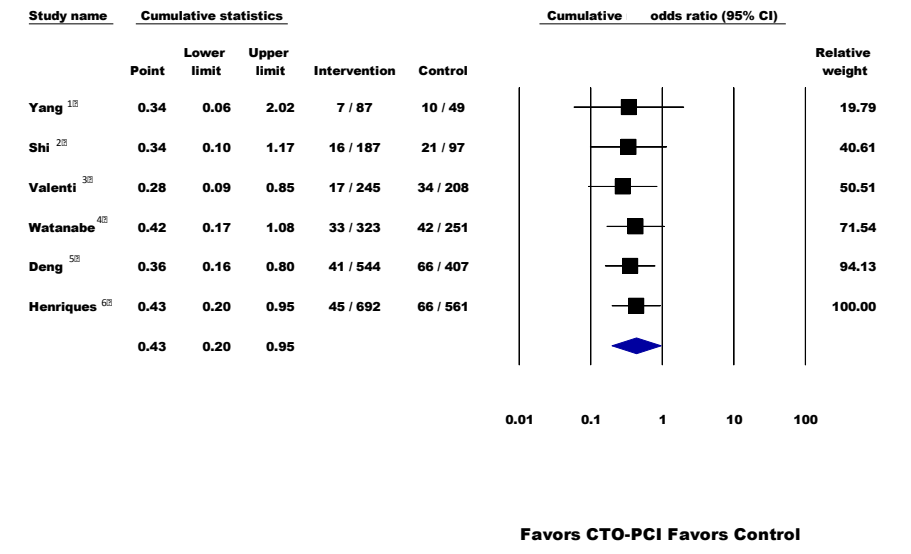
A. Major Adverse Cardiovascular Events



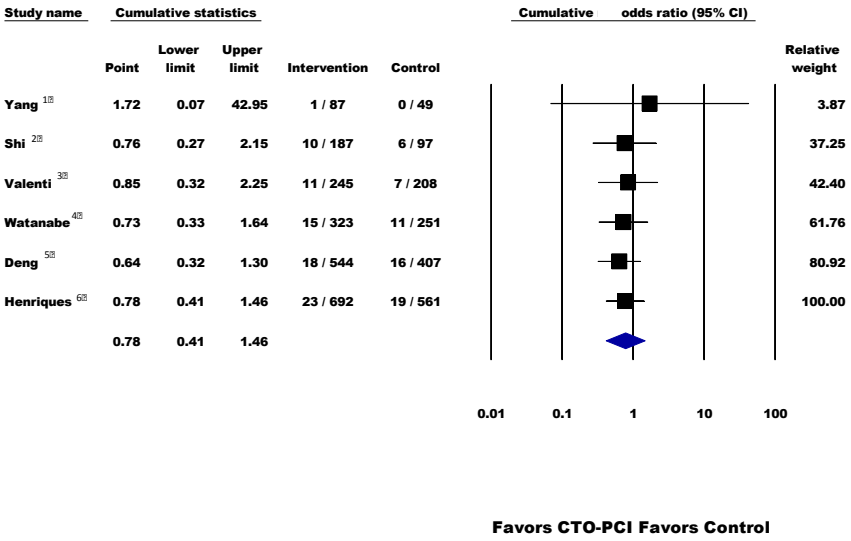
B. All-Cause Mortality



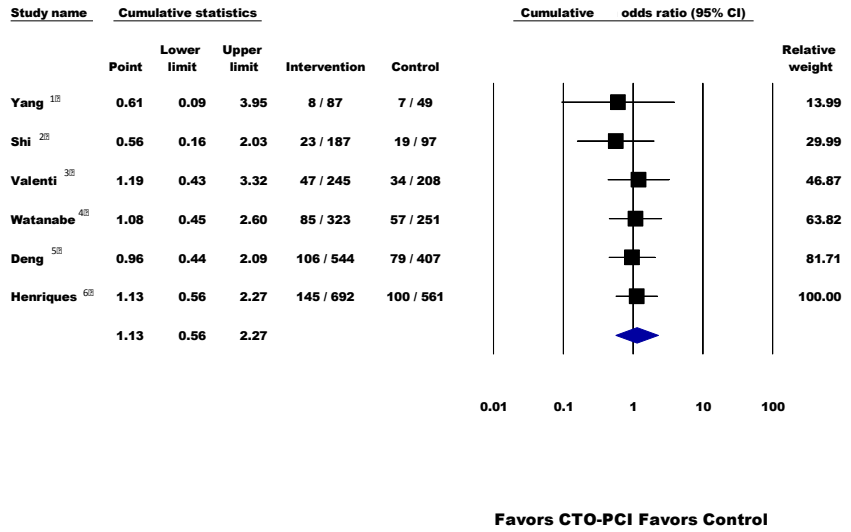
C. Cardiovascular Mortality



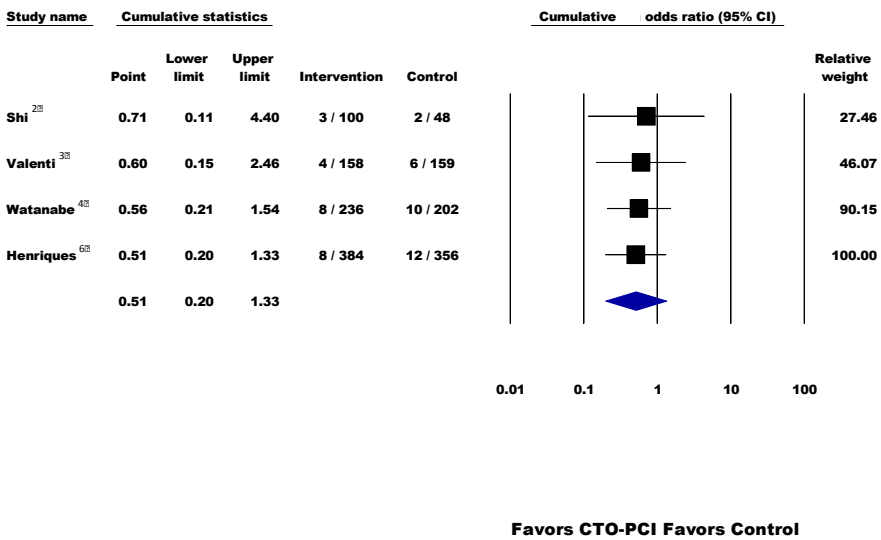
D. Myocardial Infarction



E. Repeat Revascularization



F. Stroke



G. Heart Failure

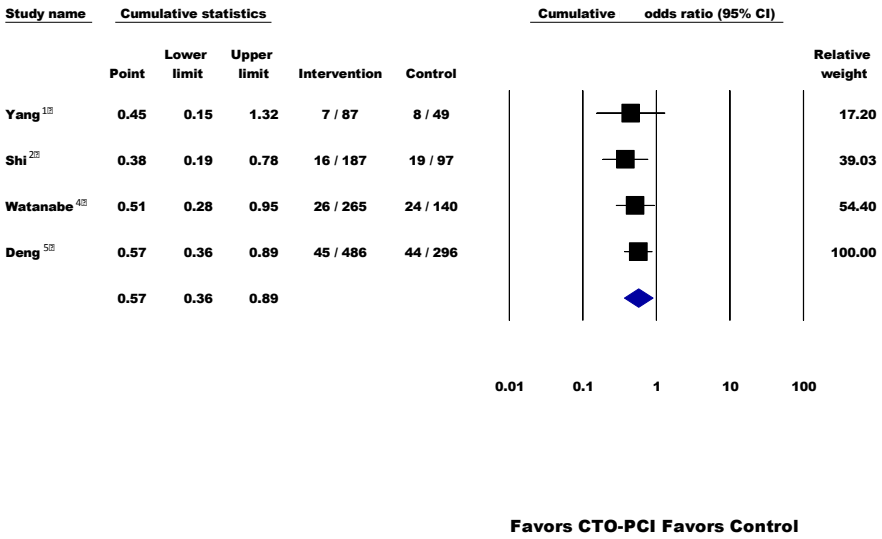
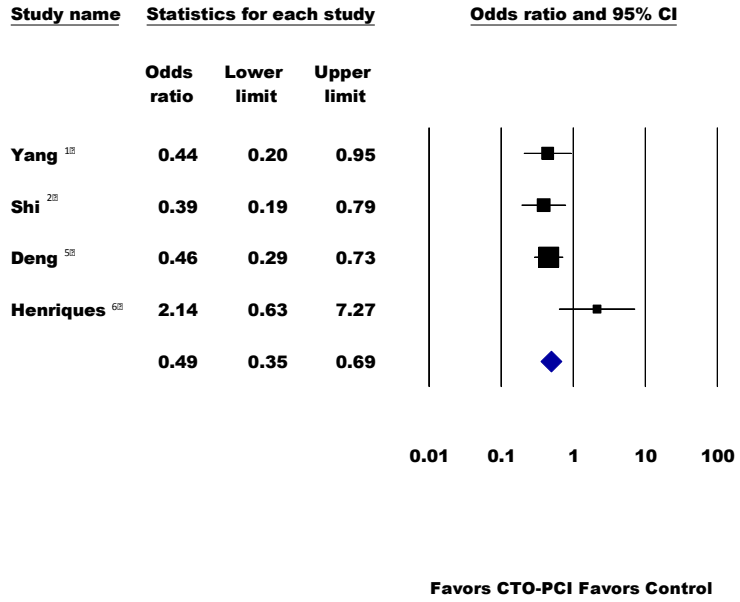
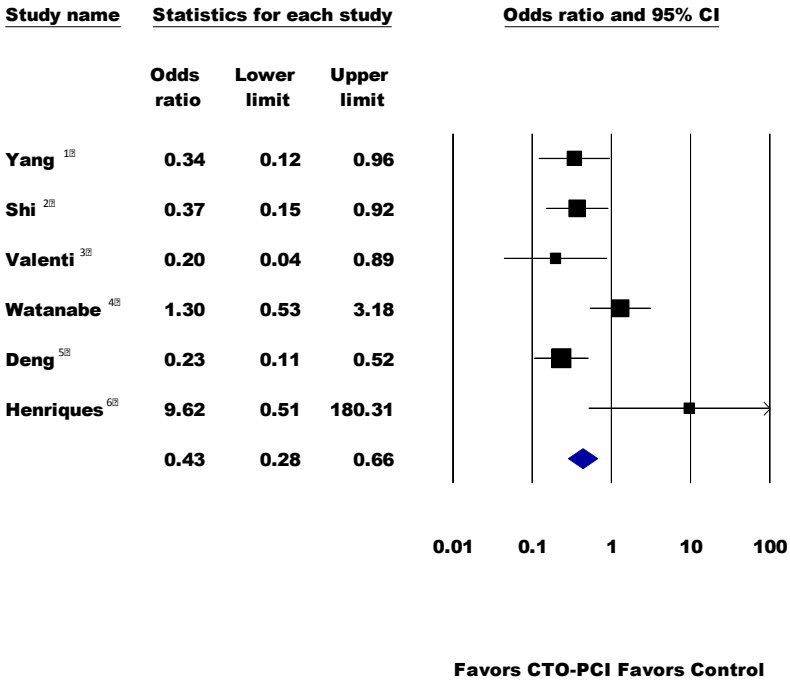


Figure S3. Sensitivity Analysis with fixed effect model.

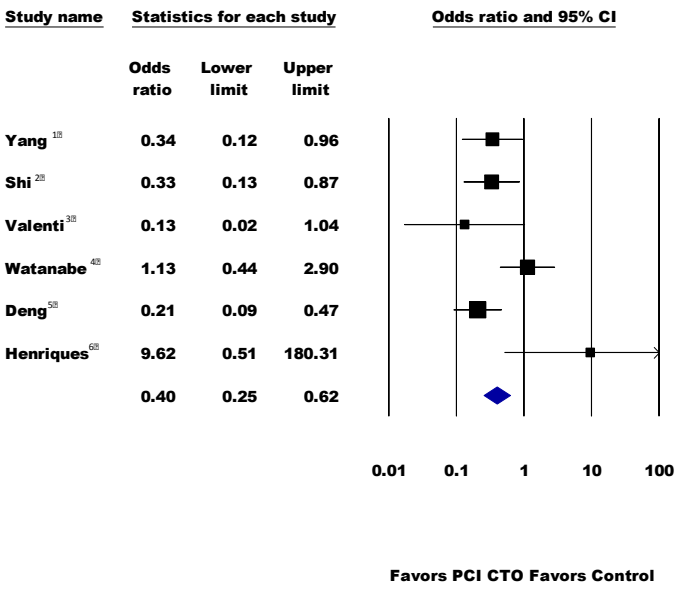
A. Major Adverse Cardiovascular Events



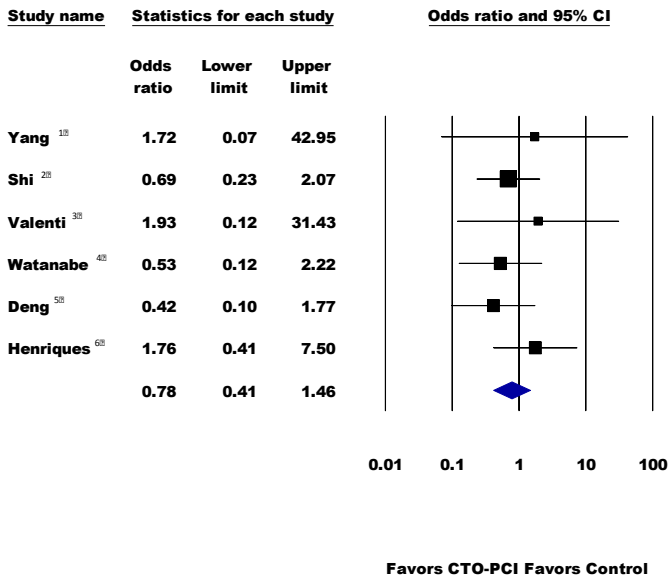
B. All-Cause Mortality



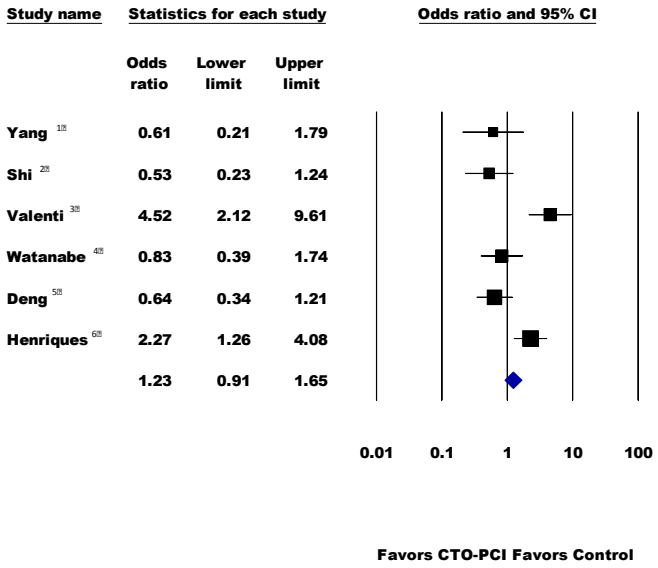
C. Cardiovascular Mortality



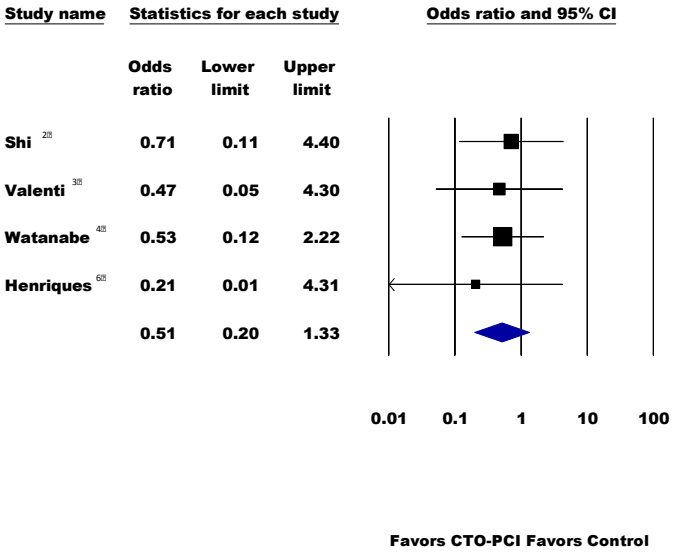
D. Myocardial Infarction



E. Repeat Revascularization



F. Stroke



G. Heart Failure

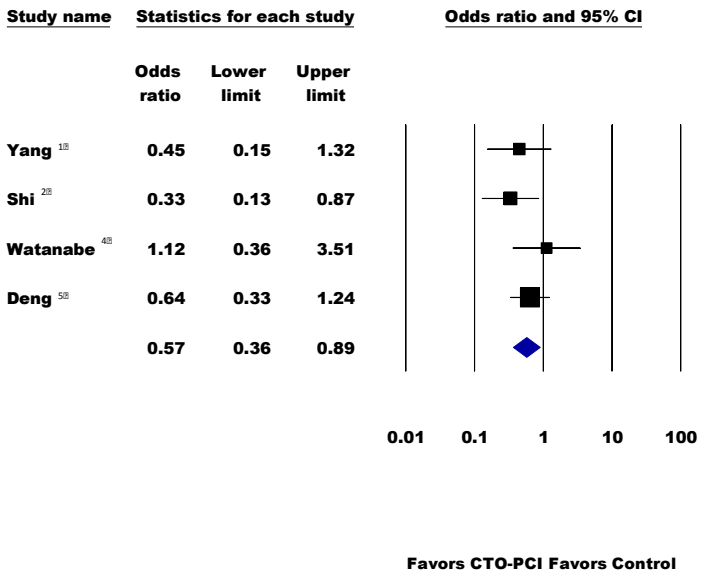
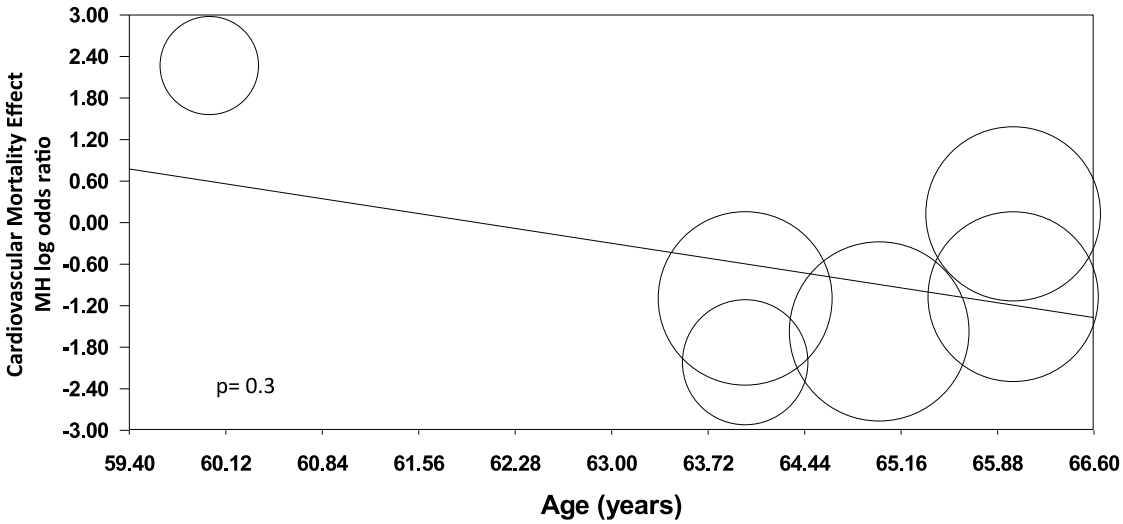
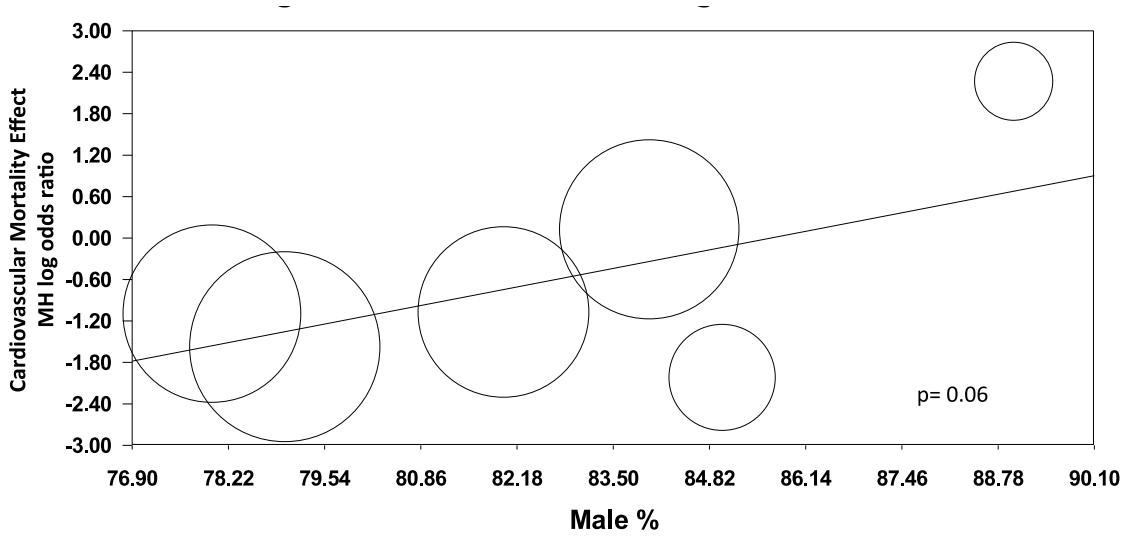


Figure S4. Meta-regression analysis by representative plots.

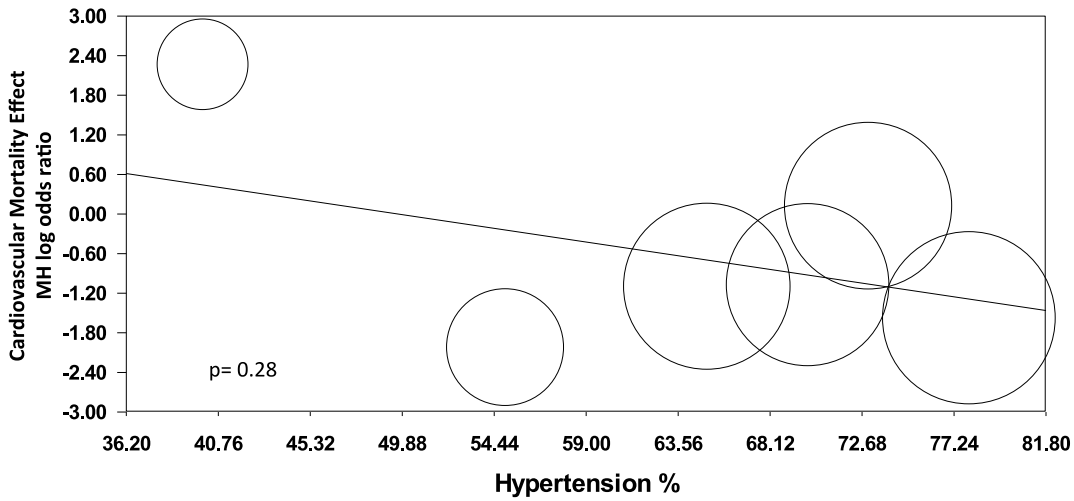
A. Age



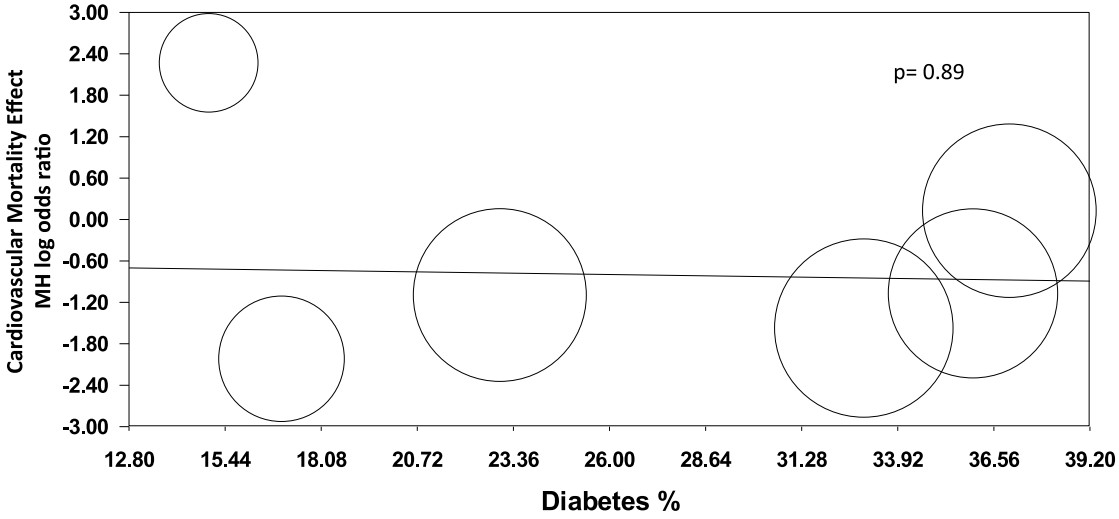
B. Male sex



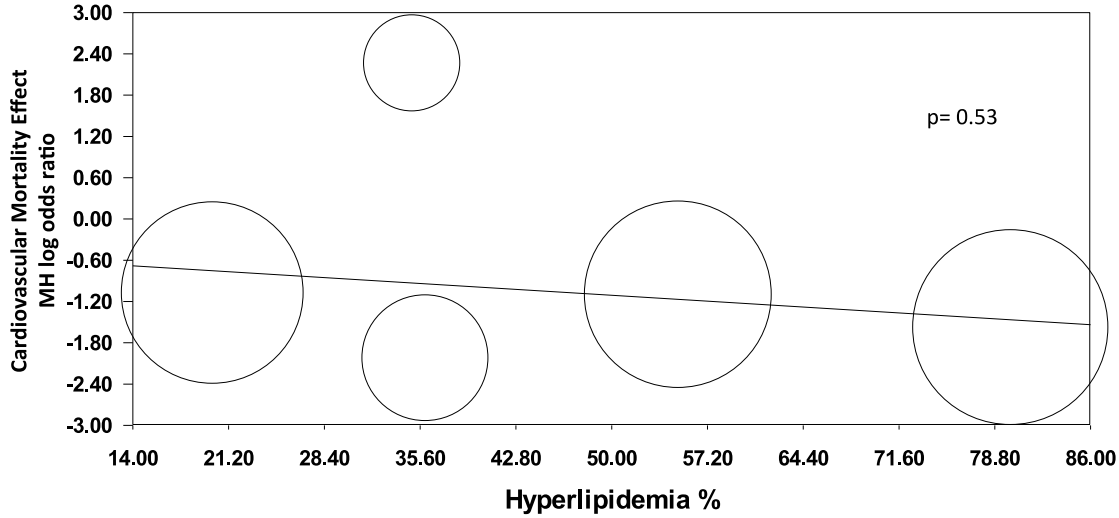
C. Hypertension



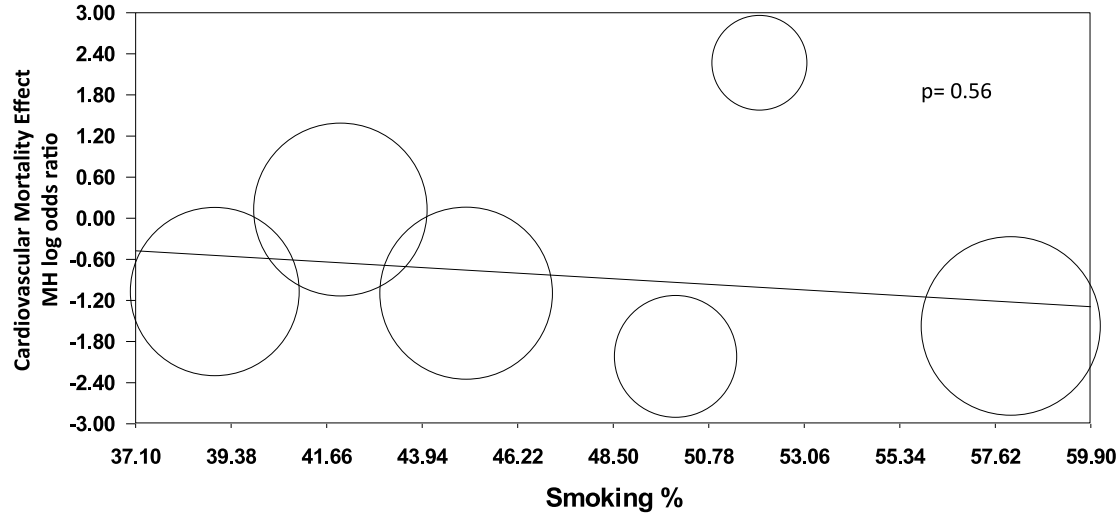
D. Diabetes Mellitus



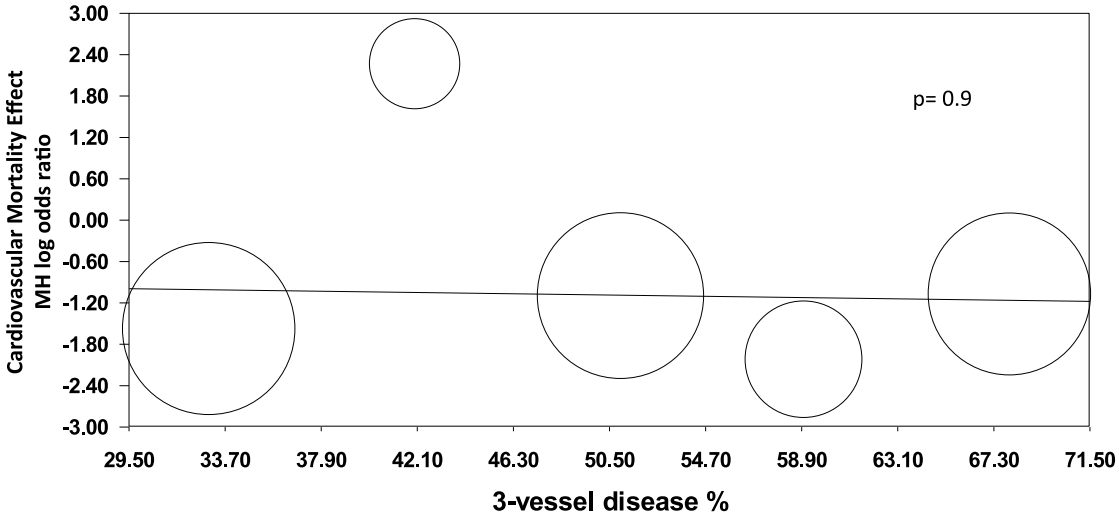
E. Hyperlipidemia



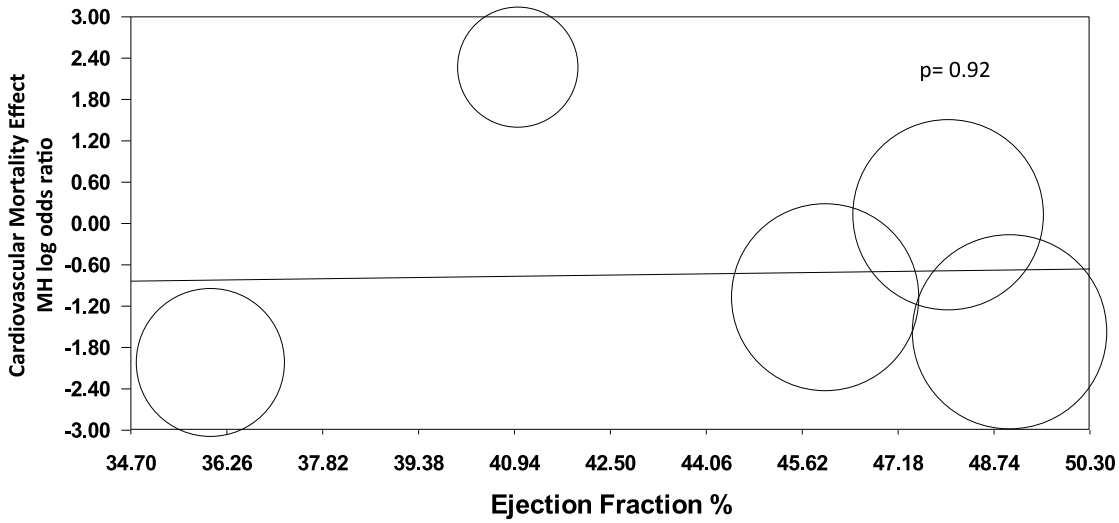
F. Smoking



G. 3-vessel disease



H. Ejection Fraction



I. CTO of the left anterior descending artery

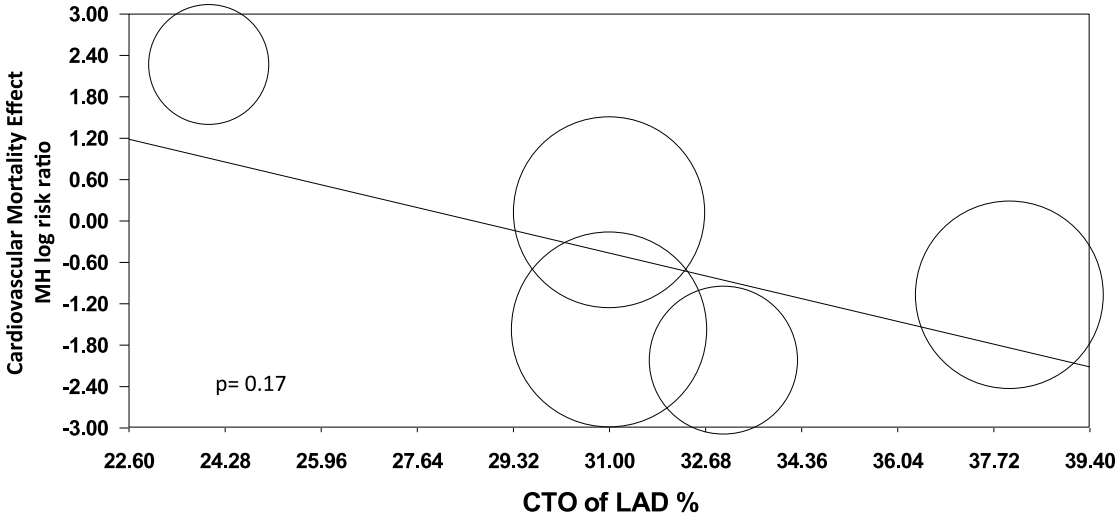
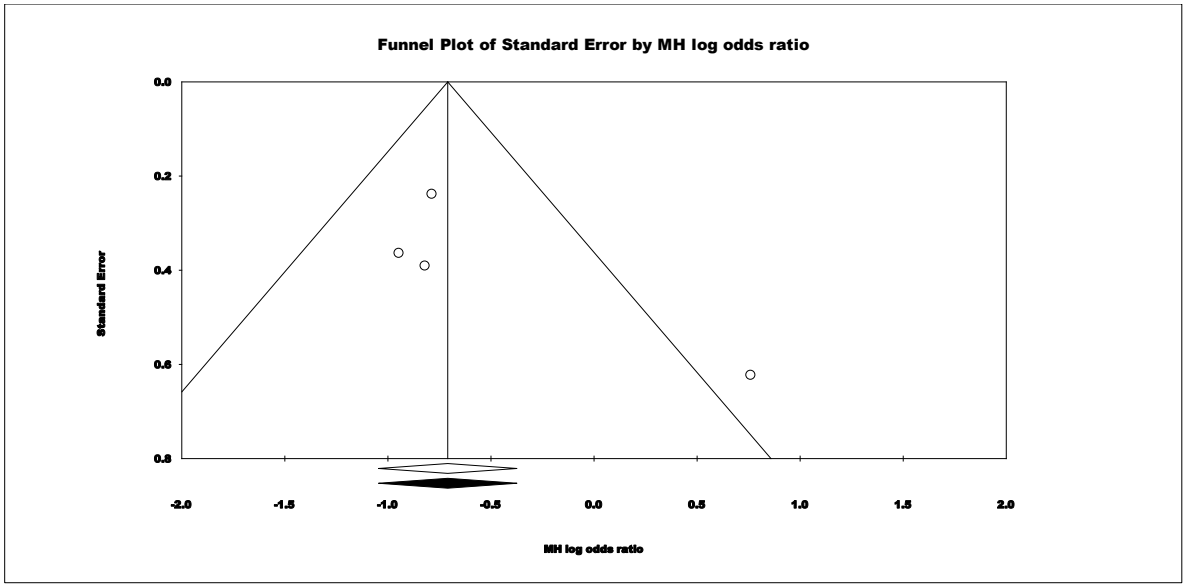
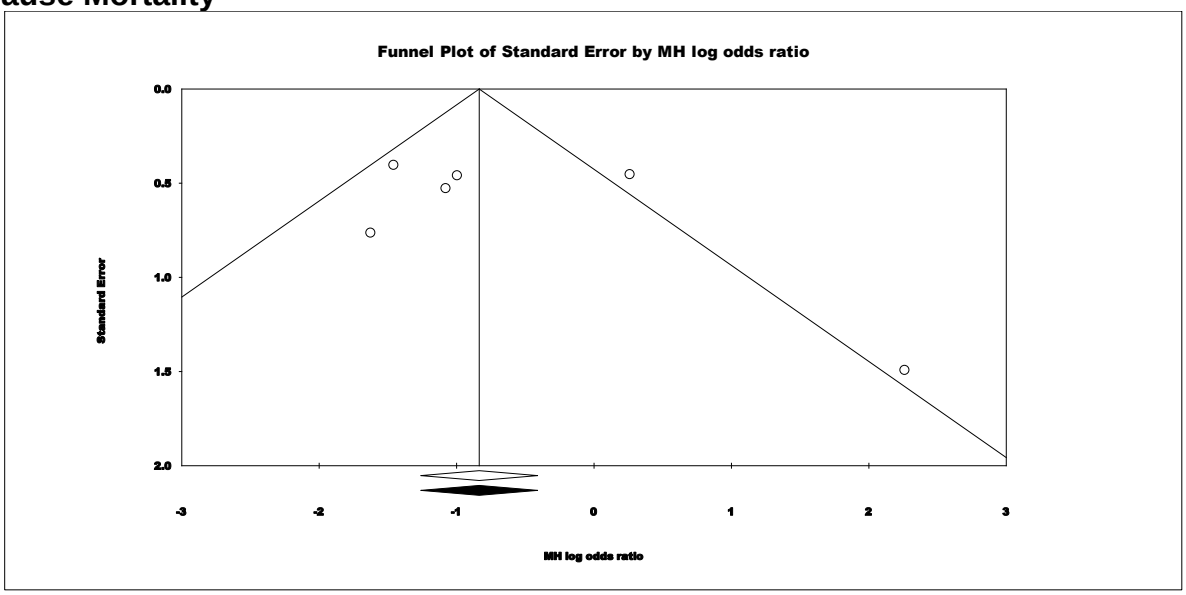


Figure S5. Funnel Plots for each outcome.

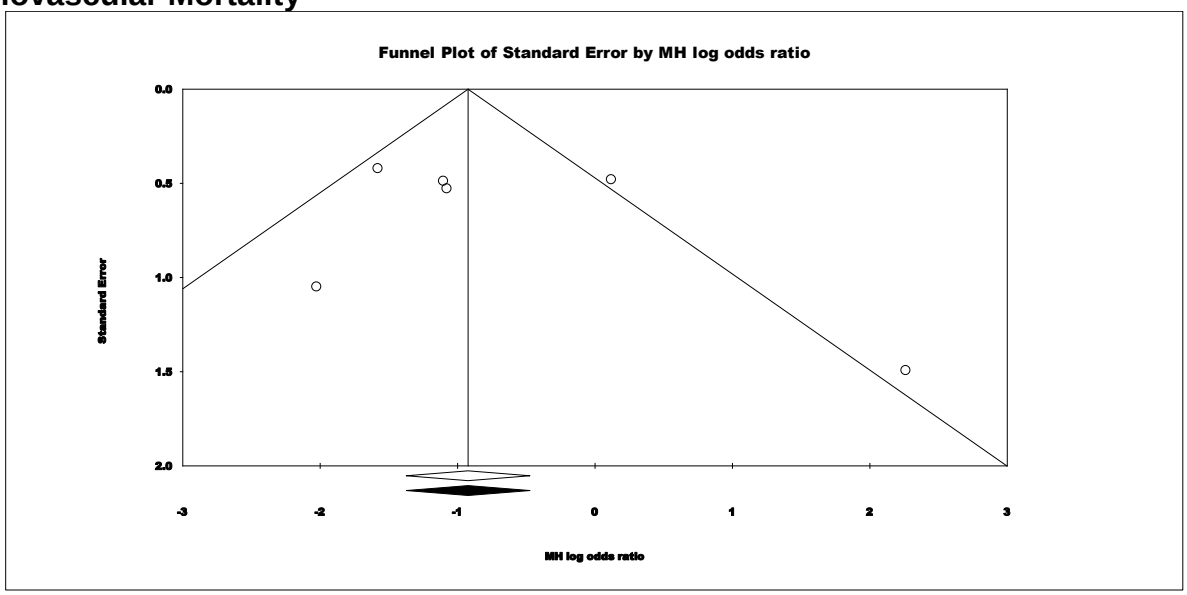
A. Major Adverse Cardiovascular Events



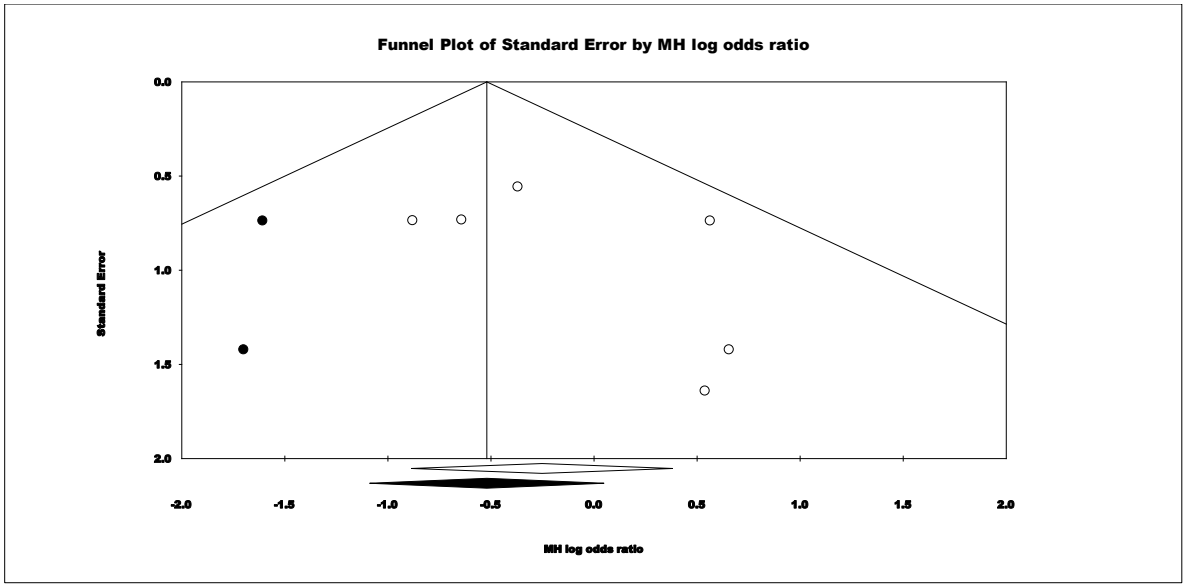
B. All-Cause Mortality



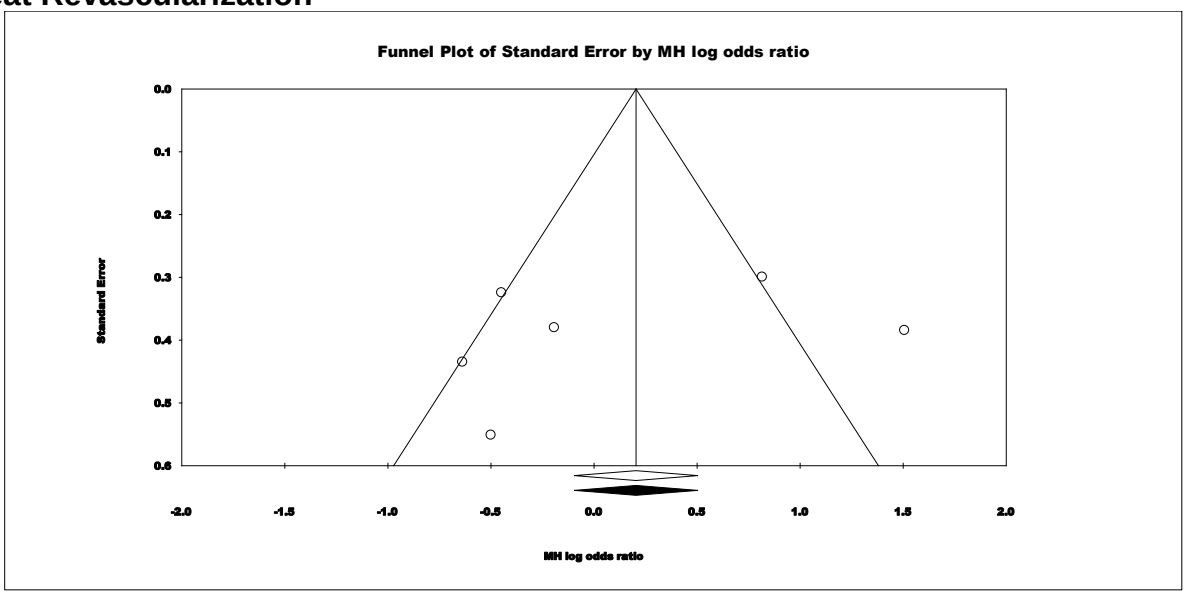
C. Cardiovascular Mortality



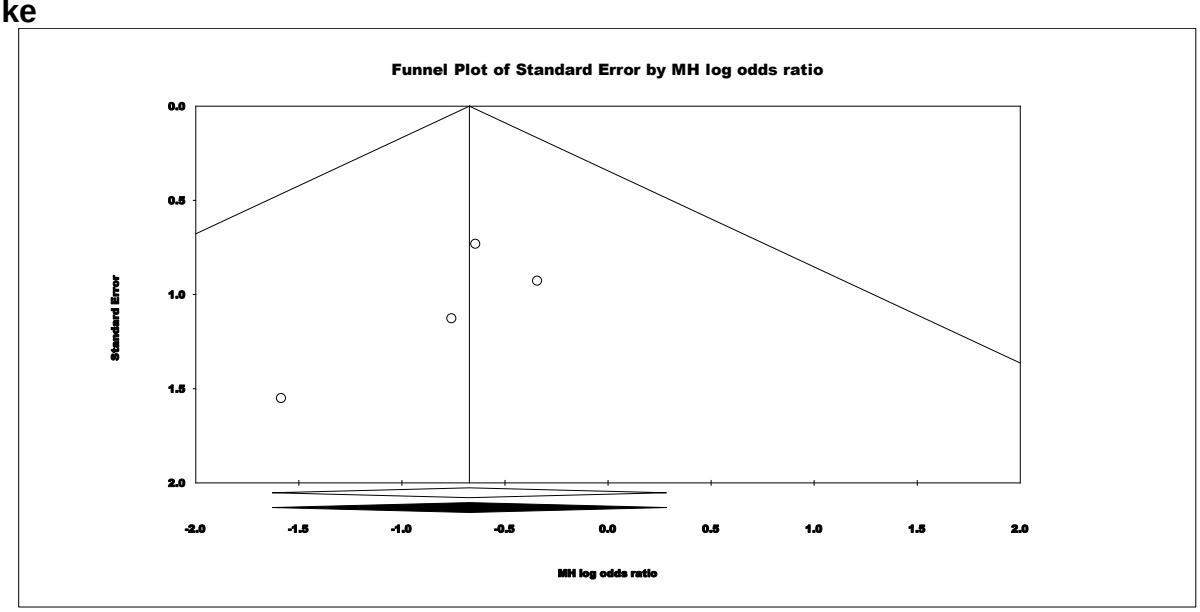
D. Myocardial Infarction



E. Repeat Revascularization



F. Stroke



G. Heart Failure

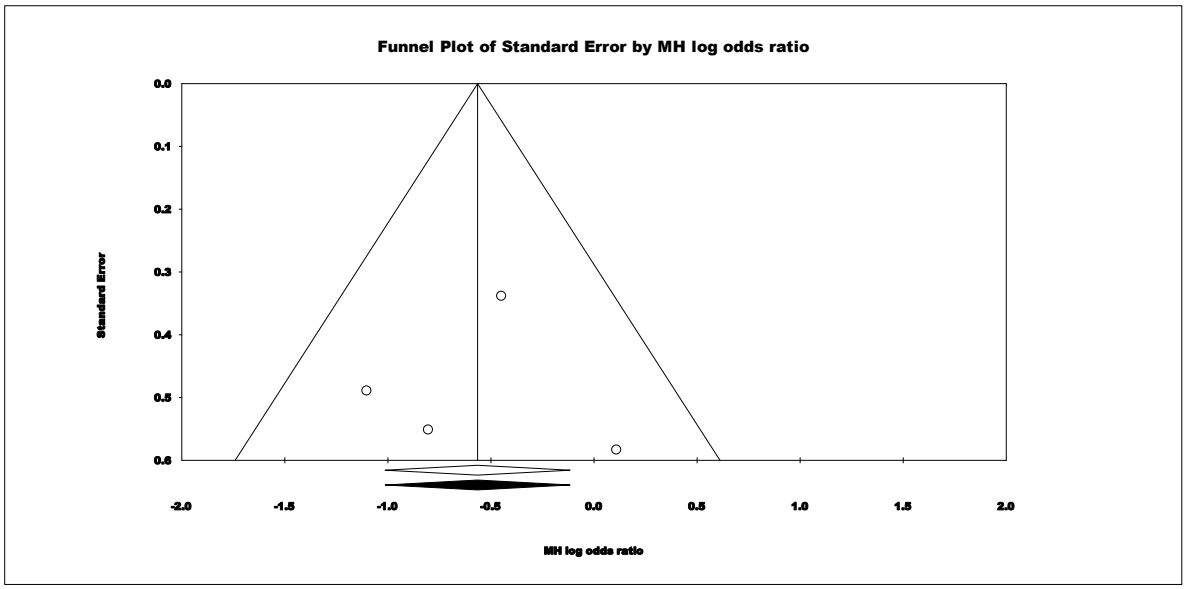


Figure S6. Quantification of Bias for each outcome using Begg and Mazumbar rank correlation, Egger's regression intercept, Duval and Tweedie's trim and fill test.

A. Major Adverse Cardiovascular Events

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	4.00000

Kendall's tau without continuity correction

Tau	0.66667
z-value for tau	1.35873
P-value (1-tailed)	0.08712
P-value (2-tailed)	0.17423

Kendall's tau with continuity correction

Tau	0.50000
z-value for tau	1.01905
P-value (1-tailed)	0.15409
P-value (2-tailed)	0.30818

Egger's regression intercept

Intercept	2.82248
Standard error	1.93455
95% lower limit (2-tailed)	-5.50120
95% upper limit (2-tailed)	11.14615
t-value	1.45899
df	2.00000
P-value (1-tailed)	0.14098
P-value (2-tailed)	0.28196

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.49182	0.35159	0.68797	0.53540	0.31619	0.90657	6.16125
Adjusted values	0	0.49182	0.35159	0.68797	0.53540	0.31619	0.90657	6.16125

B. All-Cause Mortality

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	1.00000

Kendall's tau without continuity correction

Tau	0.06667
z-value for tau	0.18787
P-value (1-tailed)	0.42549
P-value (2-tailed)	0.85098

Kendall's tau with continuity correction

Tau	0.00000
z-value for tau	0.00000
P-value (1-tailed)	0.50000
P-value (2-tailed)	1.00000

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	1.00000

Kendall's tau without continuity correction

Tau	0.06667
z-value for tau	0.18787
P-value (1-tailed)	0.42549
P-value (2-tailed)	0.85098

Kendall's tau with continuity correction

Tau	0.00000
z-value for tau	0.00000
P-value (1-tailed)	0.50000
P-value (2-tailed)	1.00000

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.43373	0.28356	0.66342	0.46831	0.21889	1.00193	13.81572
Adjusted values	0	0.43373	0.28356	0.66342	0.46831	0.21889	1.00193	13.81572

C. Cardiovascular Mortality

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	3.00000

Kendall's tau without continuity correction

Tau	0.20000
z-value for tau	0.56360
P-value (1-tailed)	0.28651
P-value (2-tailed)	0.57303

Kendall's tau with continuity correction

Tau	0.13333
z-value for tau	0.37573
P-value (1-tailed)	0.35356
P-value (2-tailed)	0.70711

Egger's regression intercept

Intercept	1.42876
Standard error	1.96083
95% lower limit (2-tailed)	-4.01539
95% upper limit (2-tailed)	6.87291
t-value	0.72865
df	4.00000
P-value (1-tailed)	0.25329
P-value (2-tailed)	0.50658

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.39713	0.25323	0.62281	0.43158	0.19588	0.95089	12.941
Adjusted values	0	0.39713	0.25323	0.62281	0.43158	0.19588	0.95089	12.941

D. Myocardial Infarction

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	3.00000

Kendall's tau without continuity correction

Tau	0.20000
z-value for tau	0.56360
P-value (1-tailed)	0.28651
P-value (2-tailed)	0.57303

Kendall's tau with continuity correction

Tau	0.13333
z-value for tau	0.37573
P-value (1-tailed)	0.35356
P-value (2-tailed)	0.70711

Egger's regression intercept

Intercept	1.01257
Standard error	0.94028
95% lower limit (2-tailed)	-1.59806
95% upper limit (2-tailed)	3.62320
t-value	1.07689
df	4.00000
P-value (1-tailed)	0.17107
P-value (2-tailed)	0.34215

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.77693	0.41248	1.46339	0.77693	0.41248	1.46339	2.90450
Adjusted values	2	0.59445	0.33683	1.04912	0.59445	0.33683	1.04912	6.42938

E. Repeat Revascularization

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-1.00000

Kendall's tau without continuity correction

Tau	-0.06667
z-value for tau	0.18787
P-value (1-tailed)	0.42549
P-value (2-tailed)	0.85098

Kendall's tau with continuity correction

Tau	0.00000
z-value for tau	0.00000
P-value (1-tailed)	0.50000
P-value (2-tailed)	1.00000

Egger's regression intercept

Intercept	-3.89586
Standard error	5.26703
95% lower limit (2-tailed)	-18.51948
95% upper limit (2-tailed)	10.72775
t-value	0.73967
df	4.00000
P-value (1-tailed)	0.25028
P-value (2-tailed)	0.50056

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		1.22605	0.90868	1.65426	1.12785	0.56010	2.27111	26.10472
Adjusted values	0	1.22605	0.90868	1.65426	1.12785	0.56010	2.27111	26.10472

F. Stroke

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-4.00000

Kendall's tau without continuity correction

Tau	-0.66667
z-value for tau	1.35873
P-value (1-tailed)	0.08712
P-value (2-tailed)	0.17423

Kendall's tau with continuity correction

Tau	-0.50000
z-value for tau	1.01905
P-value (1-tailed)	0.15409
P-value (2-tailed)	0.30818

Egger's regression intercept

Intercept	-0.98881
Standard error	0.64868
95% lower limit (2-tailed)	-3.77985
95% upper limit (2-tailed)	1.80224
t-value	1.52434
df	2.00000
P-value (1-tailed)	0.13345
P-value (2-tailed)	0.26691

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.51041	0.19632	1.32704	0.51041	0.19632	1.32704	0.47813
Adjusted values	0	0.51041	0.19632	1.32704	0.51041	0.19632	1.32704	0.47813

G. Heart Failure

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	2.00000

Kendall's tau without continuity correction

Tau	0.33333
z-value for tau	0.67937
P-value (1-tailed)	0.24845
P-value (2-tailed)	0.49691

Kendall's tau with continuity correction

Tau	0.16667
z-value for tau	0.33968
P-value (1-tailed)	0.36705
P-value (2-tailed)	0.73410

Egger's regression intercept

Intercept	-0.08401
Standard error	2.66251
95% lower limit (2-tailed)	-11.53985
95% upper limit (2-tailed)	11.37184
t-value	0.03155
df	2.00000
P-value (1-tailed)	0.48885
P-value (2-tailed)	0.97770

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.56840	0.36290	0.89028	0.56840	0.36290	0.89028	2.84170
Adjusted values	0	0.56840	0.36290	0.89028	0.56840	0.36290	0.89028	2.84170

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3. Valenti R, Marrani M, Cantini G, Migliorini A, Carrabba N, Vergara R, Cerisano G, Parodi G, Antoniucci D. Impact of chronic total occlusion revascularization in patients with acute myocardial infarction treated by primary percutaneous coronary intervention. *The American journal of cardiology*. 2014;114:1794-1800.
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5. Deng J, Wang X, Shi Y, Zhao X, Han Y. Prognostic value of the age, creatinine, and ejection fraction score for non-infarct-related chronic total occlusion revascularization after primary percutaneous intervention in acute st-elevation myocardial infarction patients: A retrospective study. *J Interv Cardiol*. 2018;31:33-40.
6. Henriques JP, Hoebers LP, Ramunddal T, Laanmets P, Eriksen E, Bax M, Ioanes D, Suttorp MJ, Strauss BH, Barbato E, Nijveldt R, van Rossum AC, Marques KM, Elias J, van Dongen IM, Claessen BE, Tijssen JG, van der Schaaf RJ, Investigators ET. Percutaneous intervention for concurrent chronic total occlusions in patients with stemi: The explore trial. *Journal of the American College of Cardiology*. 2016;68:1622-1632.