A Systematic Review and Meta-Analysis of The Long-Term Outcomes of Acute Myocardial Infarction in Preexisting Coronary Artery Ectasia

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Abstract

Background: Coronary artery ectasia is associated with an increased risk of acute myocardial infarction. This meta-analysis evaluates outcomes following acute myocardial infarction in patients with preexisting coronary artery ectasia. ***Methods:*** This meta-analysis was conducted according to PRISMA guidelines. A search strategy was designed to utilize PubMed/Medline, EMBASE, and Google scholar for studies showing the outcomes of acute myocardial infarction in patients with coronary artery ectasia from inception to February 10, 2022. We reported effect sizes as odds ratio (OR) with a 95% confidence interval (CI). We used *I*2 statistics to estimate the extent of unexplained statistical heterogeneity: *I*2 greater than 50% was considered a high degree of between-study statistical heterogeneity. ***Results:*** Of 217 studies initially identified, 7 studies comprising 13499 patients were included in the final analysis. There was no significant difference between patients with coronary ectasia and patients without coronary ectasia in terms of all-cause mortality (OR 0.95; 95% CI 0.58 to 1.56; p = 0.79; I^2=0%), MACE (OR 4.04; 95% CI 0.34 to 47.57; p = 0.17; I^2=95%), myocardial reinfarction (OR 2.13; 95% CI 0.83 to 5.47; p = 0.08; I^2=59%), target vessel revascularization (OR 1.31; 95% CI 0.69 to 2.48; p = 0.21; I^2=0%), or requiring mechanical supportive devices (OR 1.32; 95% CI 0.22 to 7.83; p = 0.57; I^2=56%). ***Conclusion:*** Acute myocardial infarction in the presence of coronary artery ectasia is not linked to an increased risk of death, major cardiovascular events, myocardial infarction, or the need for mechanical circulatory support.

Keywords: Coronary artery ectasia, coronary artery aneurysm, acute coronary syndrome, Acute myocardial infarction

1. Introduction

Coronary artery ectasia (CAE) is an aneurysmal dilatation of a coronary artery segment more than 1.5 times a nearby average segment diameter [1]. It is relatively uncommon, with an estimated 1.2% - 4.8% prevalence during coronary angiography [2]. More than 50% of the cases are secondary to coronary atherosclerosis [3]. Other causes include collagen vascular disease, sequala of childhood Kawasaki disease or iatrogenic. Most cases are asymptomatic and discovered incidentally during coronary angiography [4]. The right coronary

artery (RCA) is the most commonly involved, followed by the left anterior descending (LAD) and left circumflex (LCX). Ectasia of the left main is very rare.

The aneurysmal dilatation of the coronary produces slow and turbulent blood flow with an increased risk of acute myocardial infarction. Previous literature on outcomes following AMI in patients with CAE is inconsistent with studies showing an increased risk of recurrent MI in patients with ectatic coronary lesions [13]. Other studies showed that coronary artery aneurysms are not independently associated with worse long-term MACE or recurrent MI [14].

Furthermore, percutaneous coronary intervention in patients presenting with acute myocardial infarction and CAE has a lower success rate due to a high thrombus burden, which increases the risk of distal embolization, no-reflow phenomena and the risk of stent thrombosis [5,6]. In addition, the optimal antithrombotic regime in such patients is unclear, with limited data around optimal dual anti-platelet / anti-coagulant choice and longer-term outcomes. Therefore, the current study investigates the association between clinical outcomes and CAE in patients presenting with AMI.

2. Methods

2.1. Data source and search strategy

The present meta-analysis was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane handbook ® [7]. Studies were identified using a search strategy utilizing MEDLINE/PubMed, EMBASE and Google Scholar from inception to February 10, 2022. Two of the authors (M.M. and M.R.M.) developed a search strategy. The search included the following key terms; ("STEMI" OR " ST-elevation MI" OR “acute myocardial infarction” OR " acute coronary syndrome" OR " ACS") AND (" coronary artery aneurysm" OR " coronary ectasia").

A parallel search was also done for abstracts presented at the major scientific sessions (American College of Cardiology, European Society of Cardiology, the American Heart Association, and Society for Cardiovascular Angiography and Interventions meetings) using similar terms until February 10, 2022. We hand-reviewed the reference list of articles included in this review to include other relevant studies.

2.2. Study eligibility, selection and data extraction

Two investigators, M.M and M.R.M, initially reviewed studies based on abstracts and reviewed the full text according to eligibility criteria. The final qualification for inclusion depended on the agreement between the two reviewers. Any differences were resolved through consultation with the third reviewer (A.A).

We selected studies investigating outcomes of acute myocardial infarction in patients with preexisting coronary artery ectasia published in the English language as a full article or abstract. Patients with a previous history of CABG were excluded from selection.

We extracted data using an Excel sheet. Examples of data collected are sample size, age, male %, DM %, HTN %, Smoking %, Ectatic RCA %, Ectatic LAD %, Ectatic LCX %, Ectatic LM %, All-cause mortality, non-fatal MI, stent thrombosis, pre and post-procedural TIMI flow and hemodynamic support devices.

2.3. Outcome of interest, quality assessment and risk of bias

Primary cardiovascular outcomes were all-cause mortality, major adverse cardiac events (MACE), and myocardial reinfarction. The secondary outcomes included target vessel revascularization and the need for mechanical support devices. We assessed the quality of the included studies using the Newcastle-Ottawa Scale for cohort studies, as shown in Supplementary Table 1. For Newcastle-Ottawa Scale, each asterisk counts as one point [8]. The maximum points are two for comparability and one for all other categories (Supplementary Table 1). Each star adds to the total score. A score of less than five is considered low quality, five to six is medium quality, while seven to nine is high quality. In the included studies, two were low quality, and five were medium to high quality. We did not perform funnel plots for publication bias since the number of the included studies is less than 10 in our analysis [9].

2.4. Data synthesis and statistical analysis

Estimates in our analysis were pooled using an inverse variance random-effects model. We used the Paule–Mandel method for the estimation of $\tau 2$. We have applied Hartung–Knapp/Sidik-Jonkman small-sample adjustments considering the limited number of included studies [10]. We reported effect sizes as odds ratio (OR) with 95% confidence interval (CI). We used *I*2 statistics to estimate the extent of unexplained statistical heterogeneity: *I*2 greater than 50% was considered a high degree of between-study statistical heterogeneity [11]. We did not evaluate the publication bias as we were underpowered to detect it due to the small number of studies [12]. We performed a sensitivity analysis by excluding one trial at a time and repeating the analysis (leave-one-out analysis) for all outcomes. Given the small number of studies, meta-regression analysis was not done. We used R studio for all analyses in this study.

3. Results

The study selection process appears in (Figure 1). Seven observational studies with 13499 patients were included in the current analysis [13-19]. One of the studies was published in abstract form [18]. Details of the included studies like author, country, year of publication, sample size, mean duration of follow-up, study outcomes, and the conclusion are summarized in (Table 1). The baseline characteristics and comorbidities of the included patients are presented in (Table 2). The mean age of the included patients was 60 years, and they were predominantly men. Patients in the ectatic group were less likely to be diabetics (14%) and more likely to be smokers (63%) than in the non-ectatic group. Coronary artery ectasia was most common in RCA, followed by LAD, and less common in the left main coronary artery.

Primary outcomes:

There was no significant difference in the outcomes between patients with coronary ectasia and without coronary ectasia after acute myocardial infarction in terms of all-cause mortality (OR 0.95; 95% CI 0.58 to 1.56; p = 0.79; *I2*=0%), MACE (OR 4.04; 95% CI 0.34to 47.57; p = 0.17; *I2*=95%), and myocardial reinfarction (OR 2.13; 95% CI 0.83 to 5.47; p = 0.08; *I2*=59%). **(Figures 2-A to 2-C)**

Secondary outcomes:

In patients who underwent PCI, there was on difference in target vessel revascularization in both groups (OR 1.31; 95% CI 0.69 to 2.48; p = 0.21; *I2*=0%). The requirement for mechanical supportive devices in both groups of patients were similar (OR 1.32; 95% CI 0.22 to 7.83; p = 0.57; *I2*=56%) **(Figures 2-D & 2-E)**.

The heterogeneity was low in all-cause mortality and target vessel revascularization (I2=0%) and high in the other outcomes (I2>50%). We performed a leave-one-out analysis by excluding one trial at a time and repeating the analysis (excluding trials by the minimum I2 that can be achieved). Excluding included trials

did not change the significance of the results in any of the outcomes except for myocardial reinfarction, where excluding Doi et al. 2017 resulted in patients with coronary ectasia having higher odds of myocardial reinfarction on follow up (OR 1.59; 95% CI 1.40 to 1.82; p = 0.57; *I2*=56%). **(Figures 3-A to 3-E)**. Analysis with DerSimonian and Laird method revealed a significant increase in the risk of MACE and recurrent MI in ectasia patients (supplementary figures 1-A, 1-B)

4. Discussion

Our analysis of seven studies including more than 13,000 patients suggests that coronary artery ectasia is not independently associated with a statistically significant increased risk of long-term major adverse cardiovascular events (MACE), mortality or re-infarction in patients presenting with AMI.

Our results for the risk of cardiovascular events are supported by the findings of Baldi et al., which reported no difference in the risk of recurrent MI between the ectatic and non-ectatic patients [15]. However, they performed a propensity score weighting model and reported significantly higher rates of MI recurrence. Nevertheless, the results of individual studies are variable. Some have reported that patients with coronary ectasia are at higher risk of cardiovascular events; In a study by Wang et al., which reported the highest difference in cardiovascular events between coronary ectasia patients and the normal population, they observed a higher rate of multiple arteries ectasia reaching 65% of their sample which is nearly triple the normal reported value (25%) in other studies [13].

Of all the included articles, only Djohan et al. did not report an increased rate of MACE in the CAE group, and that might be due to the small number of CAE patients (n = 36) they included in their study, which might have influenced the power of the study [14]. Also, their patients' characteristics differed from Wang et al. and Doi et al., as they generally included younger subjects, with significant differences in the number of diabetic patients between ectatic and control patients. We conducted a sensitivity analysis by removing one study at a time, and the result was not significantly different. That is most likely because of the conservative method of analysis we used. However, using the Dersimonian and Laird method, the most commonly used method, would result in a statistically significant association ($P < 0.05$) when omitting Djohan et al. during sensitivity analysis. (Supplementary figure 1-A, 1-B). Interestingly, our effect sizes for MACE, mortality and re-infarction trended towards worse outcomes than control patients, but because of wide confidence intervals (presumably because of small sample sizes, low event rates and significant heterogeneity between some of the endpoints).

We also reported that CAE is not independently associated with higher rates of stent thrombosis in AMI patients. This finding may be counter-intuitive, as sluggish and turbulent blood flow in patients with coronary ectasia predisposes to the development of microthrombi, leading ultimately to vessel occlusion by thrombus, making PCI more challenging [20, 21]. This aligns with the results of a recently published meta-analysis indicating that coronary artery ectasia patients with STEMI had higher rates of percutaneous intervention failure (PCI) and no-reflow than non-ectatic patients [22].

The effect of co-morbidities on the development and outcomes of CAE is interesting. Diabetes has been associated with a decrease in CAE incidence in many studies [19,23,24]. This may relate to the opposing pathologies of the two conditions as diabetes affects the intimal layer of vessels causing adverse remodeling and narrowing the vessels by decreasing the synthesis and release of nitric oxide. At the same time, CAE is associated with positive remodeling of the medial layer of coronary vessels and elevated nitric oxide levels.

This unusual association with diabetes mellitus questions the belief that coronary artery ectasia is a variant of atherosclerosis-related coronary artery disease and supports the belief that CAE is part of a systemic disorder that confers ongoing chronic inflammation causing the microvascular changes observed in these patients. Hypertension and smoking are documented associated conditions of CAE. In addition, the male gender is associated with an increased risk of CAE in all the reports.

Medical treatment for CAE remains controversial. Oral anticoagulant, dual antiplatelet therapy and combinations of both have been described [26]. In the included studies, Djohan et al. reported an association between the length and diameter of ectatic segments and OAC therapy [14]. Doi et al. reported the absence of MACE during the follow-up period in patients who achieved a time-in-target therapeutic range ≥60% [17]. While Shanmugam et al. reported a decrease in MACE in CAE patients discharged on warfarin compared to CAE patients who were not [16].

Although this meta-analysis is the first to discuss the long-term outcomes of coronary artery ectasia in patients presenting with AMI, our analysis had many limitations. Firstly, the Paule-Mendele method with Hartung-Knapp adjustments, which we used for primary and sensitivity analyses, provides more conservative results. It is appropriate for the small number of included studies, as in our case, may account for why all the outcomes were non-significant between the two comparator groups. To overcome this, we provided a supplement sensitivity analysis using the most commonly used analysis method (DerSimonian and Laird) that showed statistically significant relationships. Secondly, high levels of heterogeneity were observed in most of the outcomes, which could be explained by the different characteristics of patients included in the studies. Finally, our effect size estimates suggested a four-fold increase in MACE, and a two-fold increase in myocardial re-infarction, although these were not statistically significant because of wide confidence intervals due to small sample sizes and low event rates. We, therefore, cannot completely rule out a clinically relevant increase in adverse events in patients with coronary ectasia in the setting of AMI. This deserves further investigation.

5. Conclusion

Acute myocardial infarction in the presence of coronary artery ectasia is not linked to an increased risk of death, major cardiovascular events, myocardial reinfarction, or the need for mechanical circulatory support. Larger trials are needed to look into the factors that influence the long-term outcome of CAE.

Abbreviations

CAE: coronary artery ectasia
IRAE: infarct-related coronary artery ectasia
MACE: Major adverse cardiovascular events
AMI: acute myocardial infarction
STEMI: ST elevation myocardial infarction
CABG: Coronary artery bypass graft
ACS: Acute coronary syndrome

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Figure 1: Prisma chart

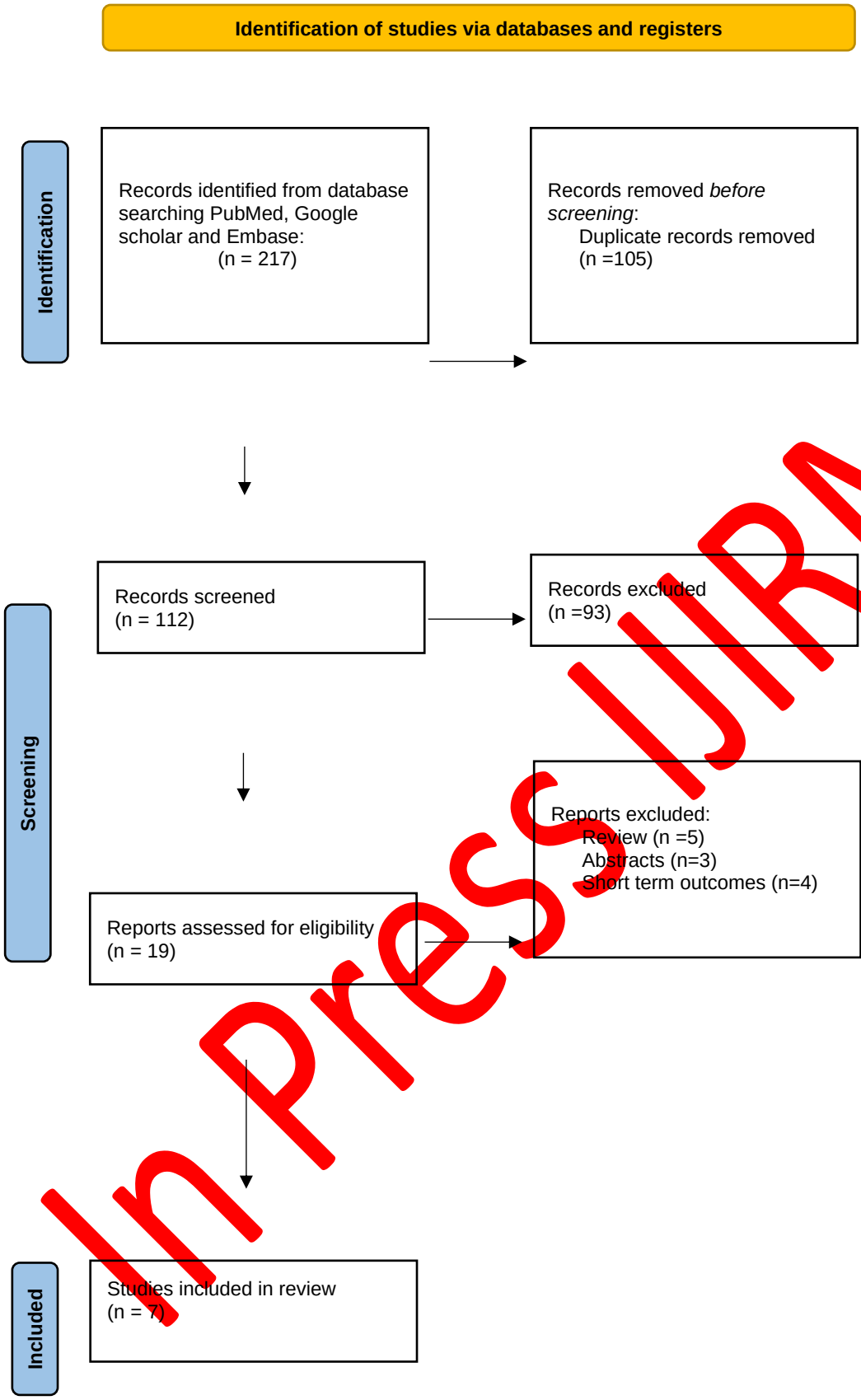


Table 1: summary of the included studies

Study	Year/Country	Design	Sample size	Mean Follow up	Outcome	Conclusion
Xu Wang [13]	2021/Netherland	Retrospective	4788	4 years	composite of (MACE) which included cardiac death, myocardial infarction, stroke and repeated coronary revascularization, including percutaneous coronary intervention or coronary artery bypass grafting.	CAE in 174 (3.6%). The presence of CAE was independently associated with an increased risk of MACE independent from cardiovascular risk factors, type of MI.
Djohan [14]	2021/Singapore	Retrospective	1789	3 years	(MACE), which consisted of all-cause mortality, unplanned repeat revascularization, myocardial infarction (MI), heart failure (HF), and stroke.	CAE in 36 (2%). CAE was not associated with unfavorable long-term outcome
Baldi [15]	2021/Italy	Retrospective	1674	4 years	Recurrent MI	-CAE in 154 (9.2%). -CAE has higher risk of recurrent MI. -No differences in terms of all-cause and cardiac death

Shanmugam [16]	2017/Australia	Retrospective	1834	3 years	Death, recurrent infarction, unstable angina, or target lesion revascularization	-CAE in 25 (1.4%) matched with 80 patients without CAE for age, gender and lesion. -CAE carries worse long-term outcomes
Doi [17]	2017/Japan	Retrospective	1689	4 years	MACE; Includes cardiac death and nonfatal myocardial infarction [MI])	-CAE in 51 (3%). -The presence of CAE predicted the future occurrence of nonfatal MI and cardiac death in the setting of AMI.
Messaoud [18]	2020/France	Retrospective	70	N.A	Hospital mortality	CAE in 47 (67%) There was no difference between the tow groups in the in hospital death
Ipek [19]	2016/Turkey	Retrospective	1655	1 year	In hospital mortality, stent thrombosis,	CAE in 99 (6%). Short-term and 1 year survival and revascularization

					cardiogenic shock	rate were similar in both groups.

Table 2: baseline characteristics

Study	Age	Male	DM	HTN	Smoking	RCA	LAD	LCA	LM
Xu Wang/2021	62±12	81.6%	6.9%	33.3%	60.3%	41.4%	32.8%	16.7%	1.7%
Djohan/2021	57.1±11.7	91.7%	11.1%	44.4%	48.2%	63.9%	25.0%	11.1%	0.0%
Baldi/2021	64.6±12	90.9%	11.7%	63.6%	72.1%	79.2%	40.3%	35.1%	2.6%
Shanmugam/2017	52.8±14.6	88.0%	0.0%	40.0%	64.0%	48.0%	32.0%	20.0%	NA
Doi/2017	63±13	84.0%	29.0%	75.0%	86.0%	76.0%	43.0%	55.0%	20.0%
Messaoud/2020	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ipek/2016	58±17	86.9%	26.3%	52.5%	49.5%	45.5%	29.3%	25.3%	NA

Figure 2-A: The forest plot of all-cause mortality

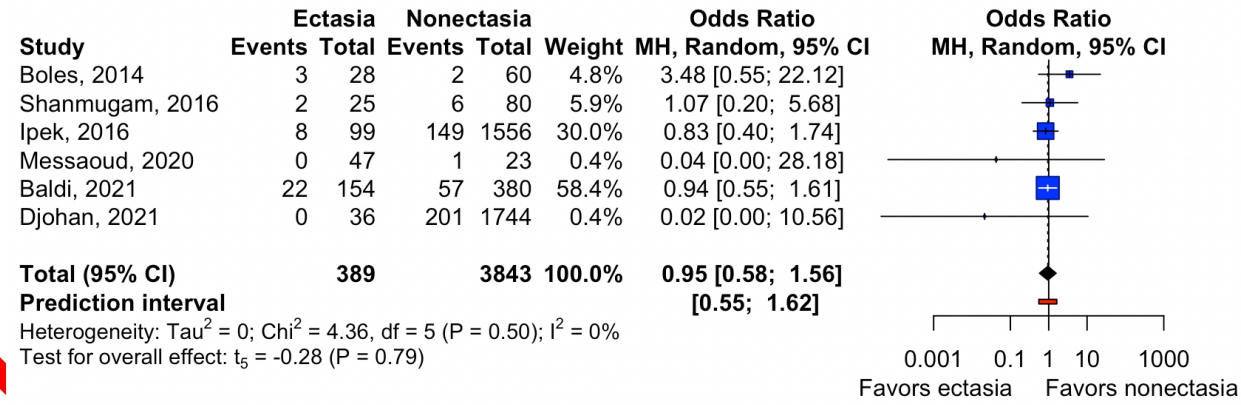


Figure 2-B: The forest plot of MACE

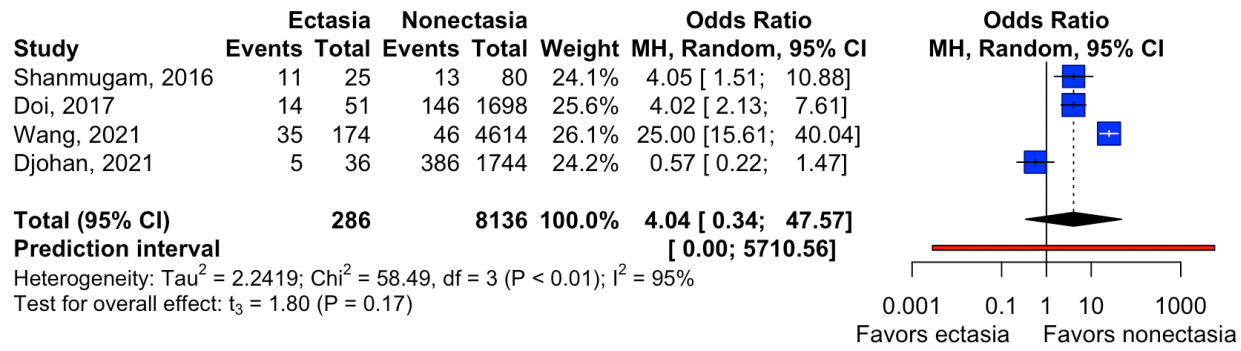


Figure 2-C: The forest plot of myocardial reinfarction

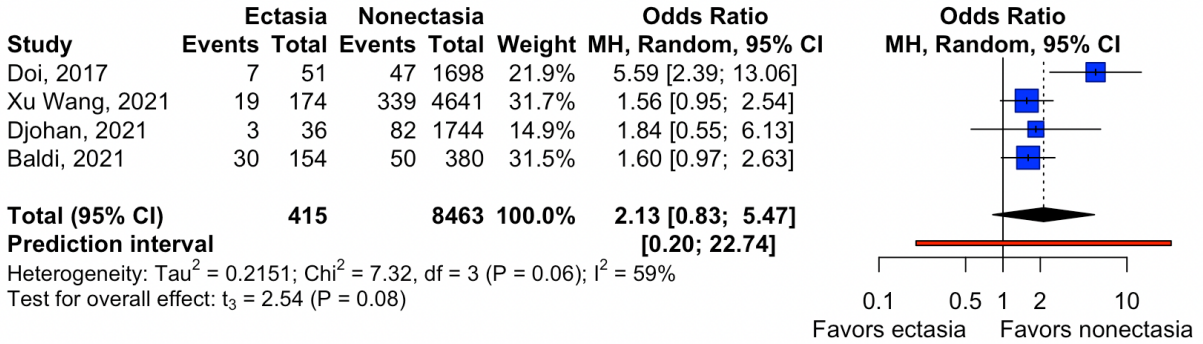


Figure 2-D: The forest plot of target vessel revascularization

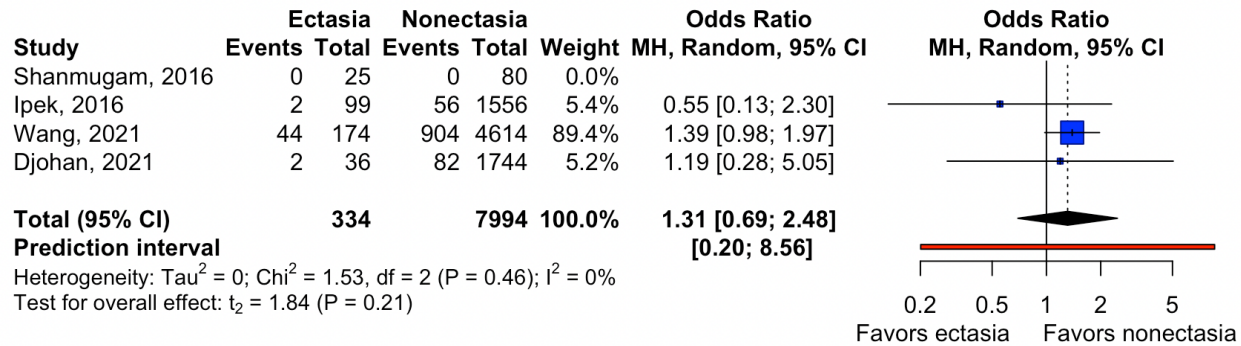


Figure 2-E: The forest plot of requiring mechanical supportive device

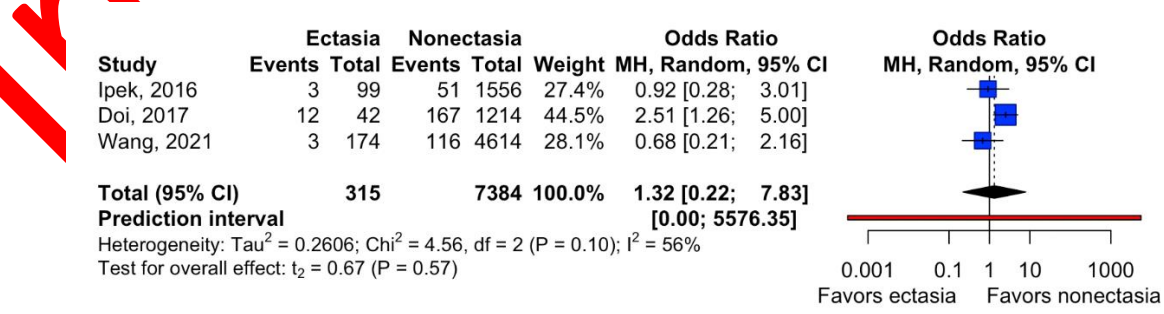
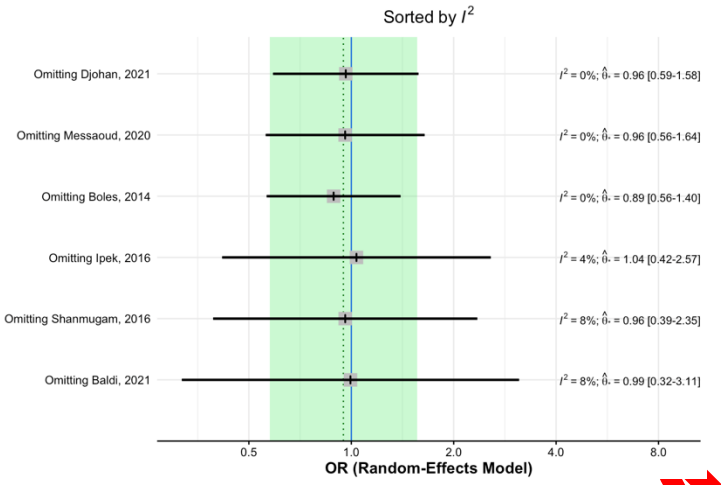


Figure 3-A: Leave-one-out analysis of mortality



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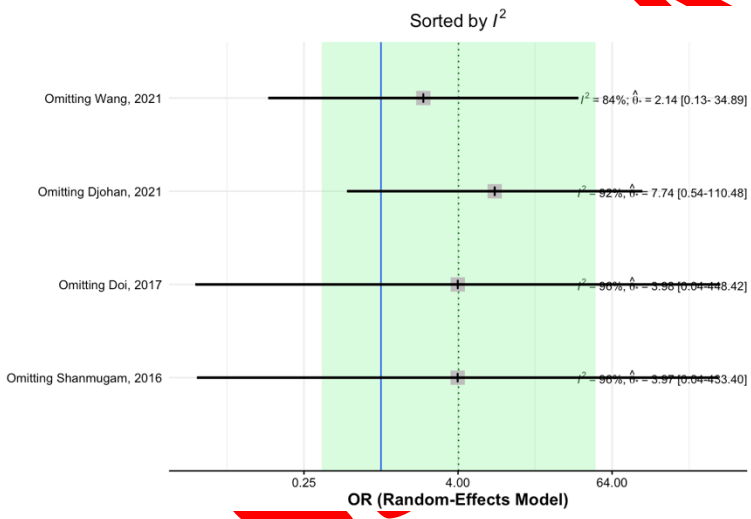
322 Figure 3-B: Leave-one-out analysis of MACE



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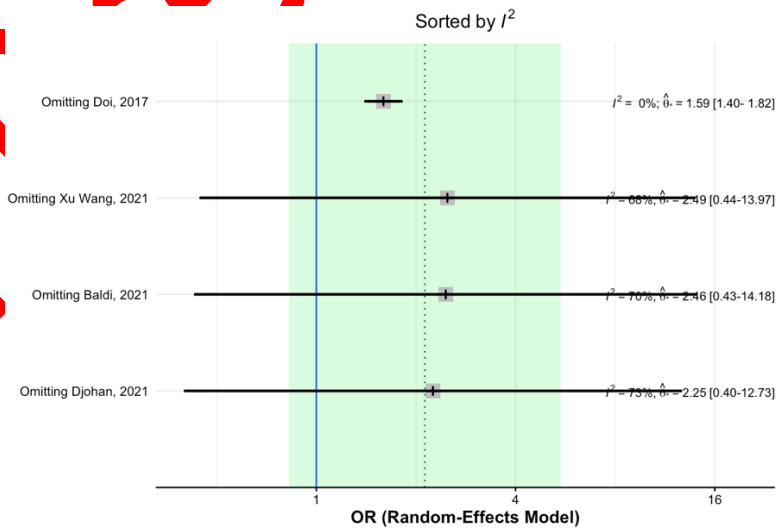
324 Figure 3-C: Leave-one-out analysis of myocardial infarction



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326 Figure 3-D: Leave-one-out analysis of target vessel revascularization

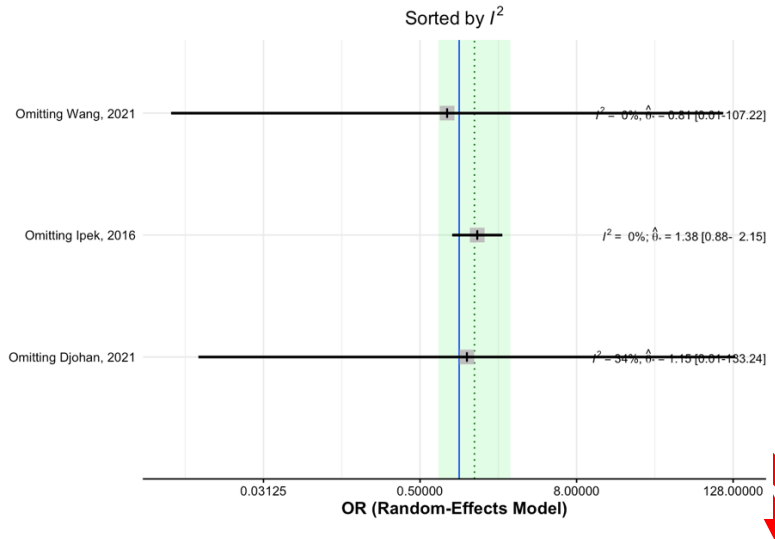
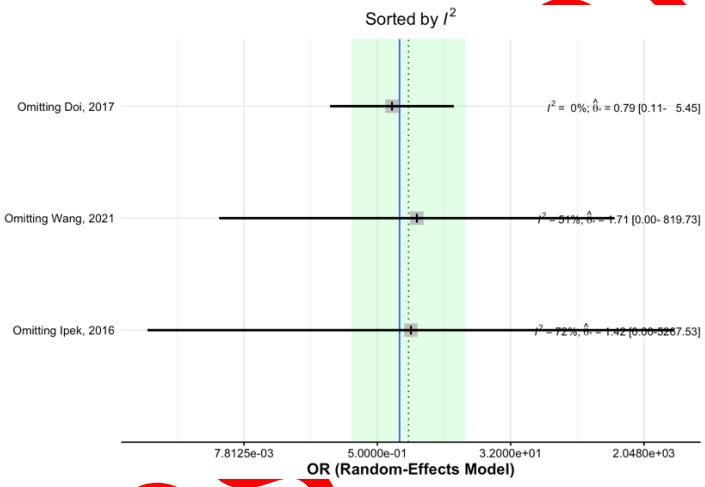


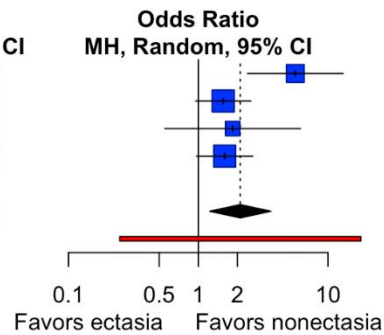
Figure 3-E: Leave-one-out analysis of requiring mechanical supportive devices



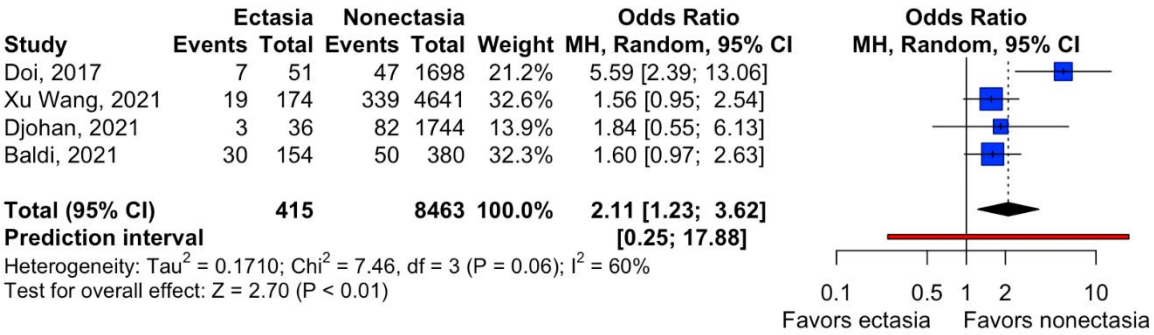
Supplementary Figure 1-A Forest plot of myocardial infarction

Study	Ectasia Events	Ectasia Total	Nonectasia Events	Nonectasia Total	Weight	Odds Ratio MH, Random, 95% CI
Doi, 2017	7	51	47	1698	21.2%	5.59 [2.39; 13.06]
Xu Wang, 2021	19	174	339	4641	32.6%	1.56 [0.95; 2.54]
Djohan, 2021	3	36	82	1744	13.9%	1.84 [0.55; 6.13]
Baldi, 2021	30	154	50	380	32.3%	1.60 [0.97; 2.63]
Total (95% CI)		**415**		**8463**	**100.0%**	**2.11 [1.23; 3.62]**
Prediction interval						**[0.25; 17.88]**

Heterogeneity: $Tau^2 = 0.1710$; $Chi^2 = 7.46$, df = 3 (P = 0.06); $I^2 = 60\%$
Test for overall effect: Z = 2.70 (P < 0.01)



Supplementary Figure 1-B: Forest plot of MACE



Supplementary Table 1: Newcastle-Ottawa scale for Quality assessment of the included studies

	Selection				Comparability		Outcome			
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	Total quality score
Baldi/2021	0	0	1	1	0	0	1	1	1	**5**
Doi/2017	0	0	1	1	1	1	1	1	1	**7**
Xu Wang/2021	0	0	1	1	0	0	1	1	1	**5**
Shanmugam/2017	0	0	1	1	0	0	1	1	1	**5**
Djohan/2021	0	0	1	1	0	0	1	1	1	**5**
Messaoud	0	0	1	1	0	0	1	0	1	**4**
Ipek/2016	0	0	1	1	0	0	1	0	1	**4**