Impact of incomplete percutaneous revascularization in patients with multi-vessel coronary artery disease: a systematic review and meta-analysis

Brief title: Incomplete revascularization in multi-vessel CAD

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Abstract

Background

Up to half of patients undergoing percutaneous coronary intervention (PCI) have multivessel coronary artery disease (MVD) with conflicting data regarding optimal revascularization strategy in such patients. This paper assesses the evidence for complete revascularization (CR) versus incomplete revascularization (IR) in patients undergoing PCI, and its prognostic impact using meta-analysis.

Methods and Results

A search of PubMed, EMBASE, MEDLINE, Current Contents Connect, Google Scholar, Cochrane library, Science Direct, and Web of Science was conducted to identify the association of CR in patients with multi-vessel coronary artery disease undergoing PCI with major adverse cardiac events (MACE) and mortality. Random effects meta-analysis was used to estimate the odds of adverse outcomes. Meta-regression analysis was conducted to assess the relationship with continuous variables and outcomes. Thirty-eight publications that included 156,240 patients were identified. Odds of death (OR:0.69, 95%CI: 0.61-0.78), repeat revascularization (OR: 0.60, 95%CI: 0.45-0.80), myocardial infarction (OR: 0.64, 95%CI: 0.50-0.81), MACE (OR: 0.63, 95%CI: 0.50-0.79) were significantly lower in the patients who underwent CR. These outcomes were unchanged on subgroup analysis regardless of the definition of CR. Similar findings were recorded when CR was studied in the Chronic Total Occlusion (CTO) subgroup (OR:0.65, 95%CI: 0.53-0.80). A meta-regression analysis revealed a negative relationship between the OR for mortality and the percentage of CR.

Conclusion

CR is associated with reduced risk of mortality and MACE, irrespective of whether an anatomical or a score based definition of IR is used, and this magnitude of risk relates to degree of CR. These results have important implications for the interventional management of patients with multi-vessel coronary artery disease.

Keywords: percutaneous coronary intervention, complete revascularization, incomplete revascularization, mortality, major adverse cardiovascular events

Introduction

Percutaneous coronary intervention (PCI) is the most common form of coronary revascularization in patients with stable coronary artery disease and acute coronary syndromes (ACS).[1] Multivessel coronary artery disease is common and affects more than half of patients who have an ACS[2,3] In these patients, there is a lack of evidence on whether revascularization that is restricted to the culprit artery is sufficient, or whether multivessel PCI would lead to an improved prognosis. Angiographically incomplete revascularization (IR) has been considered as a poor prognostic feature in multiple observational studies and post hoc analyses of randomized controlled trials[4-8] The only prospective randomized controlled trial (RCT) outside the context of ST-elevation myocardial infarction (STEMI), comparing the safety, efficacy, and costs of complete versus "culprit" vessel revascularization in multi-vessel coronary artery disease treated with PCI showed no difference in major adverse cardiovascular event (MACE) rates between the 2 strategies with a lower cost associated with the culprit only strategy in the shorter term, although costs equalized in the longer term.[9]

Recent data from randomized trials including PRAMI,[10] CvLPRIT[11] and DANAMI-3—PRIMULTI trial[12] that recruited patients presenting with STEMI undergoing primary PCI have shown that multivessel “complete” revascularization is associated with better outcomes than culprit-only revascularization. However, despite these data, important uncertainties still exist about the optimal strategy for such patients. Furthermore, in patients with stable coronary artery disease, international PCI guidelines do not provide guidance around the performance of complete revascularization (CR) versus IR, although functional assessment of lesions using non-invasive tests or fractional flow reserve (FFR) is recommended to avoid unnecessary treatment of non-significant stenosis[13-15] since this is associated with adverse outcomes.

In a previous meta-analysis by Garcia et al[16] including approximately 90,000 individuals with multi-vessel disease incomplete revascularization in 25,938 CABG patients (29% from sixteen studies) and 63,945 PCI patients (71% from twenty four publications) was associated with increased risk of mortality, myocardial infarction and repeat revascularization irrespective of the revascularization strategy employed. Since then many studies have been published including large registry data,[13,17]post hoc analyses of randomized trials[6,18,19] and observational studies[7,20-24] to assess effectiveness of complete coronary revascularization.

Our objective was to assess and update the current evidence for complete revascularization and its prognostic impact in PCI by performing a meta-analysis of 38 studies including over 150,000 patients (excluding the STEMI and surgical revascularization cohorts).

Methods

Eligibility criteria

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed[25] Studies were selected of patients who underwent PCI reporting mortality or cardiovascular events among patients with and without complete revascularization with no restriction based on study design or the indication for PCI. Publications that did not report either mortality or MACE were excluded.

Search strategy

A search of PubMed, EMBASE, MEDLINE, Current Contents Connect, Google Scholar, Cochrane library, Science Direct, and Web of Science to October 2016. We used the following search terms: “Complete revascularization” OR “Incomplete revascularization” AND “Percutaneous coronary intervention” OR PCI. These keywords were searched as text word as well as exploded medical subject headings when feasible. The search strategy example for MEDLINE is as follows 1 Complete revascularization.mp. (913), 2 Incomplete revascularization.mp. (358), 3 1 or 2 (1125), 4 exp *Percutaneous Coronary Intervention/ (31192), 5 3 and 4 (292). We excluded the STEMI and surgical revascularization cohorts. The definitions of Complete Revascularization are tabulated in table 1. Studies in all languages were included. The bibliographies of the included studies and relevant review articles were checked for additional relevant articles.

Study selection and data extraction

Two reviewers (VN and MM) independently checked all titles and abstracts for studies potentially meeting the inclusion criteria. The full reports of these studies were retrieved, and data were independently extracted on study design, participant characteristics, complete revascularization definition, outcome events, and follow-up.

Quality assessment

The Newcastle-Ottawa Scale (NOS)[26] was used as an assessment tool for selection, comparability and outcome assessment. Study quality was rated on a scale from 1 (very poor) to 9 (high). Publication bias was assessed using Egger's regression model[27] and the fail-safe number method.[28]

Data analysis

The program Comprehensive Meta-analysis (version 2.0) was used to conduct DerSimonian and Laird random effects meta-analysis.[29] Risk ratio (RR) and 95% confidence intervals (CI) were calculated. Adjusted or propensity-matched risk estimates were used when available. Meta-regression analysis was conducted to assess the relationship with continuous variables and outcomes. The Cochrane Q-statistic (I^2) was used to assess the consistency among studies, with I^2 <25% considered low, I^2 50% moderate, and I^2>75% high heterogeneity[30]

Results

Study population

A total of 425 publications were screened, then, 38 relevant studies[4-9,13,17,18,20-23,31-54] including 156,240 patients met our selection criteria (Figure 1). We excluded previous meta-analysis[16,55-67] and trials comparing target lesion revascularization versus upfront revascularization STEMI.[10-12,68-71] The studies included were mostly observational including large registries[13,17,51,54] or post hoc analyses of randomized trials like the SYNTAX trial[6] FAME trial[18] ARTS trial[31] ARTS-II Study,[44] MASS II trial[36] BARI trial[33] CABRI trial[34] and the ACUITY trial[8] Only one randomized single center trial[9] has been published so far that compares the outcomes of complete and incomplete percutaneous revascularization.

The publication dates ranged from 1988 to 2016 and the follow up period for patients ranged between one to eleven years. The numbers of patients in each study were variable and ranged between 192 to 23342 individuals. Most of these participants were male and the percent of females ranged from 7% to 37% and the mean age reported in the studies varied from 52 to 68 years. The percentage of acute coronary syndrome ranged from 0-100%.

Most of the studies used an anatomic definition for complete revascularization. Only one study used a functional definition (coronary lesions with fractional flow reserve ≤ 0.75-0.80 received a stent)[43] and seven others utilized a score based assessment(SYNTAX score a residual score of 0 is was considered to be complete revascularization) for complete revascularization.[5,6,17,19,21-23] The percentage of complete revascularization ranged from 17% to 70% with a mean of 42.7%.The study characteristics have been tabulated in table 2.

Outcomes: overall and subgroup analysis based on CR definition and Chronic Total Occlusion (CTO) revascularization

There was a significantly lower risk of death with complete revascularization (Figure 2, OR:0.69,95%CI: 0.61-0.78) among thirty-six studies[4-9,13,17,18,20-23,31-51,53,54] that reported this outcome. This lower risk of mortality was maintained after performing subgroup analysis based on the anatomic definition of complete revascularization[4,7,9,13,17,20-23,31-38,40-43,45,47-51,53,54](OR:0.69,95% CI:0.61-0.79) although this did not reach statistical significance for score based definitions[6,8,18,19,39,44,46,49](OR:0.73, 95% CI: 0.50-1.07). Similar findings were recorded in the complete CTO revascularization cohort (five studies[4,38,48,51,53](OR:0.65, 95% CI: 0.53-0.80), and in the non CTO cohort(OR: 0.71, 95% CI: 0.61-0.82).[5-9,13,17,18,20-23,31-37,39-47,49,50,54]

The outcome of repeat revascularization was reported in seventeen studies[6,8,9,13,17-20,31,33,37,41,50,54,72] there was statistically significantly lower rate in complete revascularization populations (Figure 4, OR: 0.60, 95%CI: 0.45-0.80). After subgroup analysis with respect to definition of complete revascularization this benefit was maintained in studies that used anatomic[9,13,17,20,31,33,37,41,50,54,72](OR:0.58, 95% CI: 0.41-0.82) and score based definitions[6,8,18,19](OR:0.64, 95% CI: 0.54-0.76).

Myocardial infarction was reported in seventeen studies[6,8,9,13,17-20,31,33,37,41,50,54,72] and a statistically significantly lower rate was observed (Figure 5, OR: 0.63, 95% CI: 0.50-0.79). This finding was maintained with respect to anatomic[9,13,17,20,31,33,37,41,50,54,72] (OR: 0.60, 95% CI: 0.45-0.81) and score based definitions[6,8,18,19] (OR:0.64, 95% CI:0.51-0.79) of complete revascularization.

MACE was reported in fourteen studies[6-9,13,17-20,35,39,47,54,57] and a significantly lower rate was observed (Figure 3, OR: 0.66, 95% CI: 0.51-0.85). This finding was maintained with respect to anatomic[7,9,13,17,20,35,47,57] (OR: 0.64, 95% CI: 0.46-0.89) and score based definitions[6,8,18,19,39] (OR:0.68, 95% CI:0.50-0.93) of complete revascularization.

Stent thrombosis was reported in only three studies[6,17,19,44] and there was no impact of complete revascularization in its incidence (Figure 6, OR:0.81, 95% CI:0.49-1.33).

In a subgroup analysis of two studies[8,72] that reported on outcomes in patients who exclusively had acute coronary syndromes, no significant benefit was observed (OR:0.71, 95%CI:0.44-1.11) in mortality nor MACE (OR: 0.79, 95%CI:0.54-1.17).

Regression analysis based on proportion of CR

A regression analysis was conducted and a negative relationship observed between the mortality and the percentage of CR. From the regression model, there was very strong evidence that the OR of mortality was inversely related to CR with a P value <0.001(df=34). Log OR of mortality decreased by 1.25(95% CI: -1.64 to -0.88) for every 1% increase in CR. There was no relationship between the odds ratio of mortality and year of publication.

Heterogeneity and publication bias

There was significant heterogeneity noted among the different studies that could be explained by diverse population groups. The degree of heterogeneity reduced to a minimal amount once subgroup analysis was performed based on score based definition of complete revascularization suggesting similar study designs and population cohorts. The results have been summarized in Table 4. There was no publication bias identified using the Egger's regression model.

Discussion

In our meta-analysis of 38 studies including over 156240 patients undergoing PCI, we observed that less than half of all patients with multi-vessel coronary artery disease have CR. We observed that CR is associated with a lower rate of mortality, myocardial infarction and MACE, irrespective of whether an anatomical or a score based definition of IR was used and that the magnitude of risk relates to degree of CR on meta-regression. Our analysis builds on the work done by Garcia et al[16] by placing a focus on PCI and including new studies.

There are several reasons why IR might not be achieved in PCI including patient clinical characteristics, lesion characteristics, failed PCI and operator choice. Independent predictors of IR include advanced age, race, impaired LV function, previous MI, and comorbidities such as peripheral arterial disease, heart failure, diabetes and renal failure[38] The most common lesion/anatomical characteristics for not achieving CR with PCI in SYNTAX were the presence of CTO (odds ratio [OR]: 2.46,95% CI: 1.81 to 3.39; $p<0.01$), bifurcation disease (RR: 1.44,95% CI: 1.09 to 1.89; $p < 0.01$), and diffuse disease or small vessels (<2 mm) (RR: 1.53, 95% CI: 1.12 to 2.10, $p < 0.008$).[73]

Previous studies have shown that patients with IR have a greater prevalence of adverse clinical characteristics, are older and have more complex lesions than patients with CR.[8,35,38,39,74] These adverse procedural characteristics might contribute to the associations reported. Most of the studies included in this analysis are derived from registry data, hence the decision to not undertake CR by the operator may reflect uncaptured co-morbid conditions/general frailty of the patient and so act as a surrogate of poor health status of the patients that will contribute to the poorer outcomes reported. Whilst nearly all of the studies have adjusted for differences in baseline characteristics, the possibility of unmeasured confounding, particularly in studies derived from registry data is significant. Furthermore, the increased risk associated with IR may relate to the complexity/extensiveness of coronary artery disease at baseline. For example, a post-hoc analysis of the ARTS trial revealed that IR was only associated with worse outcomes in patients in the highest SYNTAX score tertile, whereas in the low/middle tertile IR was not an independent predictor of adverse outcomes.[44]

Our analysis does not allow comparison of outcomes of patients undergoing IR in different settings such as elective versus the acute coronary syndrome (ACS) because the majority of studies do not report outcomes by clinical presentation. The subgroup analysis of acute coronary syndromes of two studies[8,72] did not show any difference in mortality or MACE between the two cohorts. The studies were heterogeneous and one of them[72] was not large enough to detect the difference among the cohorts. Nevertheless, it has been demonstrated that complete revascularization in STEMI confers survival benefit.[10-12] More recently, for example, the DANAMI-3-PRIMULTI trial reported a 44% reduction in the primary endpoint of all-cause mortality, non-fatal myocardial infarction, and repeat revascularization (HR 0·56, 95% CI 0·38–0·83; p=0.004). Following these trials multiple meta-analyses[57,64,66,75-77] have suggested a significant survival advantage in complete revascularization in patients with STEMI. Similarly, in the post hoc analysis of the ACUITY Trial[8] that included 2,954 ACS patients, IR is associated with an increased risk of major adverse cardiac events. Unstable angina accounted for approximately one third of the patients in the SYNTAX[6] and FAME trial.[18,78,79] In the *post hoc* analysis[18] of the FAME trial CR was compared to IR in patients who underwent FFR-guided PCI. There was no significant difference in survival between stable and unstable individuals at 24 months indicating a consistent treatment effect with the FFR intervention. Further, a *post hoc* analysis of the SYNTAX trial[6] performed subgroup analysis based on SYNTAX Revascularization Index <70% versus >70%. The odds ratio for patients with unstable angina was 3.25(95% CI:3.37-11.25), clearly indicating a survival advantage for patients with CR.

Our meta-regression analysis suggests that outcomes relate to the degree of CR, in agreement with several previous studies. Indeed, *post hoc* analysis of the SYNTAX trial suggests higher degrees of IR, as measured by the SYNTAX revascularization index, were associated with increased 5-year cardiac death, AMI and MACCE.[6] Similarly, Park et al[17] showed in the EXCELLENT registry that patient orientated composite endpoint rates (POCE) increased with increasing residual syntax score tertiles. Finally, CTO revascularization has been a matter of debate in recent years[51,80-82] Contemporary evidence from a large U.K. registry of 13,443 individuals with CTO[51] suggests that complete revascularization had a survival advantage over partial revascularization with a hazard ratio of 0.70(95% CI: 0.56 to 0.87). Our study confirms survival benefit regarding complete revascularization of CTO with an OR of 0.69 (95% CI: 0.61-0.78). Similarly, a meta-analysis of 7,288 patients[82] suggested that successful CTO recanalization had a survival advantage and reduced surgical revascularization.

Limitations

There several limitations associated with our analysis. Firstly, whilst we report an association between IR and adverse clinical outcomes, we cannot infer a causal relationship. Although we have shown an association between IR and adverse outcomes, it cannot be assumed that treating such patients with IR with additional PCI to attain CR would improve their prognosis. Secondly, for anatomical based definitions of IR, there are no universally accepted definitions of lesion "significance" with studies defining significant lesions as those with diameter stenosis (DS) varying between ≥ 50% and ≥ 70% in vessels of diameter ≥ 1.5mm in some studies to ≥ 2.5mm in other studies. Many of the studies included in this analysis used visual assessment to define lesion severity, which is known to have greater inter-observer variability and to overestimate percent DS compared with quantitative coronary angiograph (QCA).[83] Interestingly, a *post hoc* analysis of the ACUITY trial using QCA illustrated that even when DS≥ 30% was used to define a significant lesion, IR was independently associated with an increased risk of MACE (HR 1.36, 95%CI 1.11-1.68), although the risk increased with increasing DS thresholds (for DS threshold of ≥ 70%, HR 1.59 95% CI 1.30-1.93). Score-based definitions of IR, such as the residual SYNTAX score, overcome some of the limitations of around differences in anatomical definitions of lesion significance used across studies, allowing comparisons to be made more easily. In the current analysis, we report a similar prognostic impact of IR irrespective of whether this is defined by anatomical or score based definitions.

Thirdly, contemporary studies have shown that the functional significance of lesions on the basis of fractional flow reserve is a more important determinant of future cardiac events that anatomical/angiographic appearances[18,84-86] Operators may choose to not revascularize lesions due to their functional non-significance or location within vessels supplying infarcted and non-viable myocardium. A recent *post hoc* analysis of the FAME study[18] demonstrated that IR (as defined by residual SYNTAX score and SYNTAX revascularization index) was not associated with adverse outcome in the setting of complete functional revascularization, supporting the hypothesis that functional CR is more important than anatomical CR. The remaining studies that report outcomes following IR included in this analysis (with the exception of the aforementioned study[18]) do not differentiate between the anatomical and the functional significance of incompletely revascularized lesions. The differences in the prognostic impact of incomplete revascularization across the different studies analyzed in this meta-analysis may relate to the above limitations, mainly variability in the definition of what is considered to be a significant coronary lesion, the site of the lesion, whether the lesions that were not revascularized were in infarcted non-viable territories or were functionally significant, the sample size of the cohort studied and whether this would be adequately powered to detect a statistically significant difference and the nature of the cohort studied. Finally, most of the studies included in this analysis are derived from registry data, hence the decision to not undertake CR by the operator may reflect uncaptured comorbidity or general frailty of the patient and so act as a surrogate of poor health status of the patients that will contribute to the poorer outcomes reported. Whilst nearly all of the studies have adjusted for differences in baseline characteristics, there remains a possibility of unmeasured confounding.

In conclusion, our analysis of data derived from over 150,000 patients undergoing PCI suggests that less than half of all patients with multi-vessel coronary artery disease have CR following PCI. We observe that CR is associated with decreased incidence of mortality, myocardial infarction and MACE, irrespective of whether an anatomical or a score based definition of IR was used and that the magnitude of risk relates to degree of CR. The findings of our analysis have several practical implications for interventional cardiologists. Our reported associations between IR and adverse clinical outcomes would suggest that in patients with MVD, consideration should be given to the degree of CR that can be achieved by PCI when discussing choice of revascularization modality within the heart team, in addition to consideration of lesion complexity, functional significance, patient characteristics and syntax score in line with current international recommendations.[87] At the very least these data speak of the need for further carefully conducted randomized trials to address this question.

Contributorship

MAM conceived and planned the study. VN and SYO performed the search, screened relevant studies, extracted data from the studies and performed the analysis. MAM wrote the first draft of the paper. All authors contributed to the interpretation of the findings and reporting of the work and edited the manuscript for significant intellectual content.

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Disclosures

There are no relationships with industry.

Figure 1 Flow Diagram of included studies

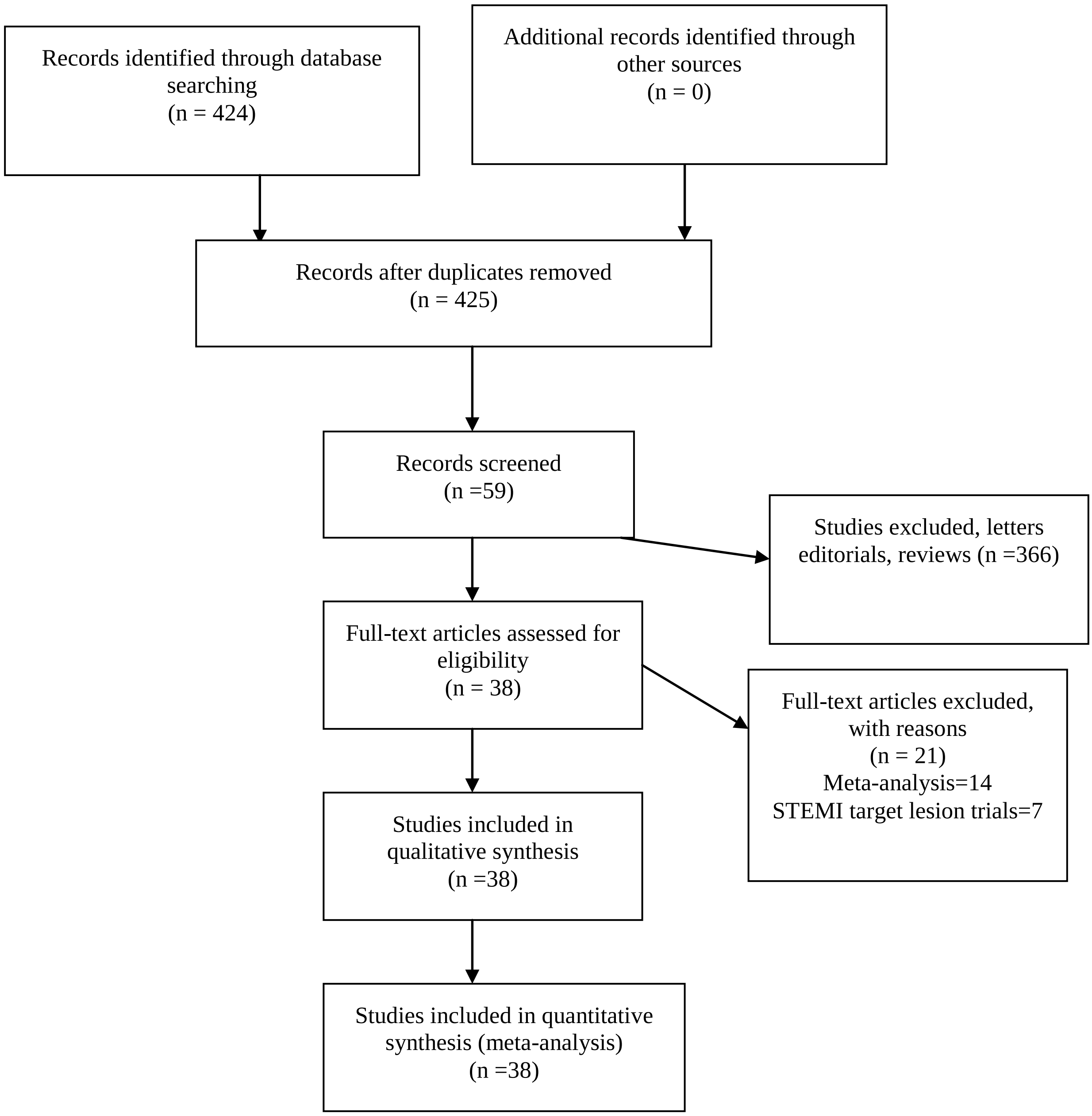


Table 1. Definitions of Complete Revascularization

Anatomical or Traditional	All diseased arterial systems with vessel size 1.5 (2.0-2.25 mm for PCI) with at least one significant stenosis > 50% receive a stent
Functional	All ischemic myocardial territories are grafted (or stented); areas of old infarction with no viable myocardium are not required to be reperfused
Numerical	Number of distal anastomosis number of diseased coronary segments/systems
Score-based	Scoring of stenosis in different vessels. Different weight given to different vessels according to number of myocardial segments supplied. A residual score of 0 is usually considered equivalent to CR
Physiology-Based	All coronary lesions with fractional-flow reserve less than or equal to 0.75-0.80 receive a stent

Table 2. Publications incorporated in the systematic review and meta-analysis

Name	Country	Year	Study type	Complete revascularization definition	Incomplete revascularization definition	Number of patients	ACS%	Follow up years	CR prevalence	% Female	Mean Age, years	NOS
Appleby et al[32]	Canada	2010	Observational study	Anatomic	Greater than 70% stenosis in epicardial vessel, assessed angiographically at the end of the procedure	12662	53	3.7	35	28	63	7
Bourassa et al[33]	USA and Canada	1999	Post-hoc analysis of the BARI trial	Anatomic: Angiographically significant lesions were defined as ≥50% stenosis in a vessel ≥1.5 mm as measured by electronic calipers	NA	896	63	5	64	23	62	6
Breeman et al[34]	Netherlands	2001	Post-hoc analysis of the CABRI trial	Anatomic: If all lesions were successfully dilated - i.e. if there were no remaining lesions with diameter stenosis <50%and incomplete otherwise.	NA	267	25	1	38	19	61	6
Capodanno et al[21]	Italy	2013	Observational study	Score-based: The baseline	Residual SYNTAX	400	62	2	48.75	23	67	6

				SYNTAX score and residual SYNTAX score were derived from the summation of the individual scorings for each lesion (defined as ≥50% stenosis in vessel ≥1.5 mm) on angiograms	score >1							
Chung et al[35]	Korea	2012	Observational study	Anatomic: Absence of diameter stenosis ≥50% in major epicardial coronary arteries or their side branches with a diameter ≥2.5 mm after successful PCI during index admission irrespective of the function or viability of relevant myocardium	NA	845	28	3.9	66.3	36.8	64	6
D'Oliveira Vieira et al[36]	Brazil	2012	Post-hoc analysis of the MASS II trial	Anatomic	NA	192	0	10	36	33	59	8
Deligonul et al[37]	USA	1988	Observational study	Anatomic: Successful dilation of all major	NA	397	49	2	59	24	NA	6

				coronary, or branch vessels and absence of residual stenosis ≥50% in a major coronary vessel.								
Gao et al[7]	China	2013	Observational study	Anatomic: Angiographic CR, which entailed successful angioplasty of all diseased lesions in the major epicardial coronary vessels and their first degree side branches (diameter ≥2.5 mm);	Patients not meeting the definition of CR were defined as having IR. divided into four subgroups: (1) 1 IR vessel with no total occlusion; (2) 1 IR vessel with total occlusion; (3) ≥2 IR vessels with no total occlusion, and (4) 2 IR vessels with total occlusion.	7065	61.2	1.3	16.8	20.94	58	7
Généreux et al[6]	Multicenter	2015	Post-hoc analysis of the SYNTAX trial	Score-based: The baseline SYNTAX score and residual SYNTAX score were derived from the summation of the individual	The SYNTAX Revascularization Index was calculated with the following formula: (Δ	903	28.5	5	43.5	23.7	65	8

				scorings for each lesion (defined as ≥50% stenosis in vessel ≥1.5 mm) on angiograms	SS/ baseline SYNTAX score × 100). Classified into SRI = 100% SRI 50% to <100% SRI <50%							
Hambraeus et al[13]	Sweden	2015	Observational study	Anatomic	Defined as any nontreated significant (at least 60%) stenosis in a coronary artery supplying >10% of the myocardium	23342	80	1	35	27.2	68.1	7
Hannan et al.[4]	USA	2006	Observational study	Anatomic: defined as attempting all lesions with ≥50% stenosis in major epicardial coronary vessels (proximal, mid, and distal right coronary artery, left anterior descending, and left circumflex) either during the index hospitalization or any time within 30 days after discharge from the	Patients not meeting the definition of CR were defined to have IR.	21945	NA	3	31	31	NA	6

				index hospitalization but before suffering a new myocardial infarction.								
Hannan et al.[38]	USA	2009	Observational study	Anatomic: Defined as successfully attempting all diseased (≥70% stenosis) lesions in major epicardial coronary vessels (proximal, mid, and distal segments; major left anterior descending diagonals; and circumflex marginal branches) with PCI either during the index hospitalization or at any time within 30 days after discharge from the index hospitalization for PCI but before suffering a new MI. Success was defined as a reduction in stenosis of at least 20% and a residual	Patients not meeting the definition of CR were defined to have IR.	11294	37	1.5	31	33	NA	6

				stenosis of less than 50%.								
Ijsselmuiden et al[9]	Netherlands	2004	RCT	Anatomic: Randomly assigned to undergo PCI of either the coronary artery thought to be responsible for ischemia (culprit vessel) or of all ≥50% stenosis (complete revascularization).		219	37	5	50	26	62	9
Kobayashi et al[18]	Multicenter	2016	Post-hoc analysis of FAME trial	Score-based: The baseline SYNTAX score and residual SYNTAX score were derived from the summation of the individual scorings for each lesion (defined as ≥50% stenosis in vessel ≥1.5 mm) on angiograms	Residual SYNTAX score of 0, >0 to 4, >4 to 8, and >8, and with SYNTAX revascularization index of 100%, 50% to <100%, and 0 to <50%.	427	31.9	2	14.5	25.5	64.7	8
Kim et al[39]	Korea	2011	Observational study	Anatomic: Angiographic CR-1, according to the SYNTAX classification, was defined as angioplasty or grafting in all diseased coronary	Patients not meeting these criteria were considered IR patients.	1400	42	5	41	29	61	6

				segments (≥1.5 mm), consisting of the right coronary artery (segments 1, 2, and 3) and its main branches, including the posterior descending artery (segment 4 or 15) and the posterolateral branch (segment 16); the left anterior descending artery (segments 5, 6, 7, and 8) and its major diagonal branches (segment 9 or 10); and the left circumflex artery (segments 11 and 13) and its major obtuse marginal branches (segment 12 or 14).11–13 Angiographic CR-2 was defined as revascularization in all diseased segments ≥2.5 mm in diameter.								
Kip et al[40]	USA	1999	Post-hoc	Anatomic:		2047	NA	5	59	NA	61	6

			analysis of the BARI trial	Angiographically significant lesions were defined as >50% stenoses in a vessel >1.5 mm, as measured by electronic calipers. A reduction in stenosis of ≥20% with residual stenosis of <50% and TIMI grade 3 flow defined successful lesion dilation.								
Kloeter et al[41]	Switzerland	2001	Observational study	Anatomic: no remaining main coronary artery stenosis of >50%.		250	NA	2.5	60	18	59	6
Malkin et al[22]	United Kingdom	2013	Observational study	Score-based; SYNTAX score and residual SYNTAX score were derived from the summation of the individual scorings for each lesion (defined as ≥50% stenosis in vessel ≥1.5 mm) on angiograms	Residual SYNTAX score of >0	353	53	3.4	48.7	NA	68	7
Malkin et al[23]	United Kingdom	2013	Observational study	Score-based; SYNTAX score and residual	Residual SYNTAX score of >0	240	38	2.6	41	26	66.9	7

				SYNTAX score were derived from the summation of the individual scorings for each lesion (defined as ≥50% stenosis in vessel ≥1.5 mm) on angiograms								
Mariani et al[72]	Italy	2001	Observational study	Anatomic: defined as successful management of all significant stenoses in major epicardial vessels, while incomplete revascularization (IR) was defined as the residual presence of .>50% stenosis in a major segment after the procedure		208	100	1	24	17	63	6
Nikolsky et al[42]	Israel	2004	Observational study	Anatomic	NA	658	22	3	27	27	61	6
Norwa-Otto et al[43]	Poland	2010	Observational study	Functional: Complete revascularisation was defined as successful PCI of all coronary artery lesions with significant narrowing not fulfilling the above	Functionally driven IR was defined as dilation of all segments with >70% stenosis, with the exception of arteries supplying an	908	33	11	31	18	52	6

				criteria.	area of previous transmural myocardial infarction (MI) or a small amount of myocardium.							
Park et al[17]	Korea	2014	Observation al study	Score-based: The baseline SYNTAX score and residual SYNTAX score were derived from the summation of the individual scorings for each lesion (defined as ≥50% stenosis in vessel ≥1.5 mm) on angiograms	Residual SYNTAX score of 0, >0 to <7, and >7	5088	64.5	1	42.7	32	62	7
Rosner et al[8]	USA	2012	Post-hoc analysis of ACUITY trial	Anatomic	Was variably defined as any lesion with a final DS ranging from ≥30% to ≥70% (in 10% increments) with a reference vessel diameter (RVD) ≥2.0 mm by QCA was left	2954	100	1	63	31	60	8

					untreated after PCI in any epicardial coronary artery.							
Sarno et al[44]	The Netherlands	2010	Post-hoc analysis of the ARTS-II Study)	Anatomic: Patients were considered to have complete revascularization if all lesions with >50% diameter stenosis had been successfully treated.	Those patients in whom attempt was made to treat 1 significant lesion or whose treatment resulted in a final diameter stenosis >50% were considered to have incomplete revascularization.	567	45	5	61.2	23	62.5	6
Sohn et al[20]	Korea	2014	Observational study	Anatomic: CR was defined as the absence of ≥70% diameter stenosis in major epicardial coronary arteries or their branches with a diameter ≥2.0 mm after successful PCI		263	29	3.3	57	25.8	67	6
Song et al[45]	Korea	2012	Observational study	Anatomic: CR strategy was defined as		873	48	1.5	48.9	30	64	6

				attempting all lesions with >50% stenosis in major epicardial coronary vessels and their major branches during the index hospitalization								
Srinivas et al[46]	USA	2007	Observational study	Anatomic: CR required that at least one lesion had to be treated in each of the major territories with diameter stenosis >50%.		1406	36.5	1	22	33	62	6
Tamburino et al[47]	Italy.	2008	Observational study	Anatomic: Revascularization was defined as complete, when all lesions with >50% diameter stenosis located in segment of at least 2.25 mm diameter, by quantitative coronary analysis, were successfully treated either during the index hospitalization or staged electively within 3 months after the initial		508	50	3	42	21	62	7

				procedure.								
Valenti et al[48]	Italy	2008	Observational study	Anatomic: Complete revascularization was defined as a restoration of TIMI grade 3 flow with residual stenosis <30% on visual assessment in the three coronary arteries and their major branches (branch diameter ≥2 mm).		486	37.5	2	62	17	68	6
Van den Brand et al[31]	Multicenter	2002	Post-hoc analysis of the ARTS Trial	Anatomic: if all lesions of ≥50% diameter stenosis had been successfully treated.	If no attempt was made to treat one or more significant lesions, or if treatment resulted in a final diameter stenosis ≥50%, these patients were considered to be incompletely revascularized.	576	38	1	70	21	61.5	8
Wu et al[5]	USA	2011	Observational study	Anatomic: R was defined as reduction of stenosis to <50%	When a CR was not achieved during a	13016	NA	8	30	31	NA	6

				in all diseased (≥70% stenosis) lesions in major epicardial coronary vessels (left anterior descending artery and major diagonals; left circumflex artery and large marginal branches; and right coronary artery and right posterior descending artery) in the index hospitalization or within 30 days after discharge from the index hospitalization before having a new MI. However, if they had an MI before the CR was completed, this was not regarded as CR because of the occurrence of an adverse event before CR was attained.	stenting procedure, it was defined as a procedure with IR.							
Wu et al[49]	USA	2014	Observational study	Anatomic: CR was defined when the post-procedural	When CR was not achieved after the	21767	NA	5	31.4	33.5	NA	7

				stenosis in each of the lesions was reduced to < 50% in the index hospitalization or within 30 days in staged PCI procedures following discharge from the index hospitalization before the occurrence of a new MI.	stenting procedure in the index admission or within 30 days of discharge, the revascularization was defined as incomplete revascularization (IR)							
Yang et al[50]	China	2010	Observational study	Anatomic: Clinical lesions were defined as > 50% stenosis of a main coronary artery, or > 70% stenosis of its primary branches. The definition of CR was the treatment of all lesions in the main coronary artery and primary branches.	Incomplete coronary revascularization (ICR) was defined as treatment of main culprit lesions but not other clinical lesions.	324	92	1.5	22	22	61	6
George et al[51]	UK	2014	Observational study	Successful PCI to the target CTO and post-procedural obstruction of <50% in all major epicardial coronary	Successful PCI to the target CTO but with residual obstruction of >50% in $1	13443	NA	2.65	NA	21	63.5	6

				arteries.	other vessels.							
Hannan et al[52]	USA	2016	Observational study	Defined as a residual stenosis of <50% for all lesions with preprocedural stenoses of at least 70%. The reference category for the variable was successful CTO PCI and CR of all other lesions with preprocedural stenosis of at least 70%. Also, if a CTO or non-CTO PCI was successful in a staged admission, that patient was regarded as having undergone a successful PCI.	NA	4030	NA	1.8	61	22.4	63.2	6
Danzi et al[53]	Italy	2013	Observational study	Defined as a TIMI flow grade 3 with residual stenosis of <30% on visual assessment in the 3 coronary arteries and their major branches (branch diameter of >2 mm).	NA	120	33.3	2	63.3	7.5	68	6

Chang et al[54]	South Korea	2016	Prospective cohort study	Absence of diameter stenosis ≥50% in major epicardial coronary arteries or their side branches with a diameter ≥ 2.5 mm after successful stent implantation during index hospitalization irrespective of the function or viability of relevant myocardium	Not meeting the CR criteria	3901	54.1	4.9	50	30	63	8

Table 3. Results of studies that evaluated incomplete revascularization and adverse outcomes

Name	Results
Appleby et al[32]	Better survival with complete revascularization (87±1% versus 78±1%, P<0.001). Residual disease significant independent predictors of the need for repeat procedures.
Bourassa et al[33]	CR (n 579) (%) IR (n 317) (%) p Value Death 87.5 84.0 0.13 MI 83.8 84.1 0.91 Repeat revascularization 46.3 42.8 0.48 Angina 79.8 75.6 0.22
Breeman et al[34]	At one month PTCA Remaining lesions 0 1 2 ≥3 Death (%) 2.1 0.7 0.8 2.5 Ml (%) 4.9 2.8 3.3 5.0 (Repeat revascularization) CABG (%) 2.8 1.4 7.4 20.2 (Repeat revascularization) PTCA (%) 4.2 3.5 5.7 5.9 At one year PTCA Remaining lesions 0 1 2 ≥3 Death (%) 5.4 2.0 3.3 5.0 Ml (%) 5.4 3.4 4.9 6.7 (Repeat revascularization) CABG (%) 7.4 9.5 18.0 37.0 (Repeat revascularization) PTCA (%) 25.0 22.5 23.8 19.3
Capodanno et al[21]	Cardiac mortality at 2 years were 3.3%, 4.5%, and 19.8% in the complete revascularization.
Chung et al[35]	Propensity score-matched (n=550) Adjusted HR [95% CI] Death 0.66 [0.34–1.28] Death and MI 0.51 [0.28–0.95] Death, MI, and repeat revascularization 0.84 [0.60–1.19] Cardiac death 0.50 [0.18–1.40] Cardiac death and MI 0.39 [0.16–0.96] Any adverse cardiac events 0.93 [0.64–1.35]
D'Oliveira Vieira et al[36]	A statistically significant difference was observed for the PCI group (CR, 6 individuals died, IR 20 individuals died)
Deligonul et al[37]	Outcomes Events/CR Total Events/IR Total Repeat revascularization CABG/PTCA 24/118,73/255 MI 3/118, 9/255 Death 6/118, 14/255
Gao et al[7]	At 36 months, cardiac death was significantly greater in the IR cohort (2.55% vs. 1.13%, log-rank test: P=0.016), but there was no difference in the 3-year rates of MI, TVR, and MACE between the two cohorts. Angiographic IR had a greater risk of cardiac death (adjusted hazard ratio [HR]: 2.56, 95% confidence interval [CI]: 1.03–6.41)
Généreux et al[6]	At 60 months, rates of MACE were linked with IR.

Hambraeus et al[13]	Unadjusted HR (IR compared with CR) repeat revascularization 2.05 (95% CI: 1.80 to 2.32; $p < 0.0001$), combined endpoint of death/MI, HR was 1.92 (95% CI: 1.77 to 2.09; $p<0.0001$) for IR compared with CR.
Hannan et al.[4]	Adjusted HR for IR patients comparative to CR patients for death was 1.15 (95% CI, 1.01 to 1.30). Repeat revascularization: 10.09% for CR patients and 11.46% for IR patients (P=0.16).
Hannan et al.[38]	(IR vs CR) 18-month mortality (adjusted HR: 1.23, 95% CI: 1.04 to 1.45) and 18-month MI/mortality (adjusted HR: 1.27, 95% CI: 1.09 to 1.47). The adjusted survival rates for CR and IR were 94.9% and 93.8% (p=0.01) and the freedom from MI rate was 93.3% and 91.7% (p = 0.002).
Ijsselmuiden et al[9]	(IR vs CR) MACE rates at 1 month (14.4% vs 9.3%), 1 year (32.4% vs 26.9%), and 4.6 ±1.2 years (40.4% vs 34.6%) were similar in both cohort.
Kobayashi et al[18]	Patients with MACE had comparable RSS and SRI after PCI (RSS: 6.0 [IQR: 3.0 to 10.0] vs. 5.0 [IQR: 2.0 to 9.5], p =0.51 and SRI: 60.0% [IQR: 40.9% to 78.9%] vs. 58.8% [IQR: 26.7% to 81.8%], p = 0.24, correspondingly). Kaplan-Meier analysis showed comparable 12-month rate of MACE with different RSS/SRI (log-rank p = 0.55 and p = 0.54, correspondingly).
Kim et al[39]	(CR vs IR) MACE HR 0.82 (95% CI: 0.58-1.15), MACCE HR 0.90 (95% CI: 0.75-1.09)
Kip et al[40]	Outcomes Events/CR Total Events/IR Total Repeat revascularization 328/59, 237/399 Death 55/595,47/399
Kloeter et al[41]	Outcomes Events/CR Total Events/IR Total Repeat revascularization 10/101 23/149 MI 1/101 1/149 Death 0/101 3/149 Complete revascularization had considerably higher clinical restenosis (35 vs. 22%, P=0.02)
Malkin et al[22]	Complete revascularization was significantly linked with survival (Adjusted OR 3.1 95%CI: 1.7–5.6)
Malkin et al[23]	Outcomes Events/CR Total Events/IR Total Death 6/98 29/142 P value<0.001
Mariani et al[72]	Outcomes Events/CR Total Events/IR Total Repeat revascularization 1/49 7/159 MI 4/49 5/159 Death 0/49 2/159 In-hospital MACE occurred in 10% and 7.5% of patients with CR and IR, correspondingly (P = NS). At 12-months, the reported MACE was 11.3% and 11.5% of patients with CR and IR, correspondingly.
Nikolsky et al[42]	Survival in CR was 94.5%, rivaled to 83.0% for those

	with IR (p<0.001). MI-free survival was considerably greater in patients with CR against IR (92.9% vs. 79.9%, correspondingly). IR was prognosticator of mortality (95% CI, 1.54-7.69; p=0.003).
Norwa-Otto et al[43]	There was no difference in mortality, cardiovascular deaths or MI between CR and IR cohorts. The IR had a higher rate of repeat revascularization.
Park et al[17]	Outcomes Events/CR Total Events/IR Total MACCE 114/2173 297/2915 Death 28/2173 65/2915 Myocardial infarction 4/2173 19/2915 Unplanned revascularization 86/2173 225/2915 Definite/probable stent thrombosis 11/2173 21/2915
Rosner et al[8]	(IR vs CR) Unadjusted HR (95% CI) for IR vs CR: Death 1.43 (0.90–2.27) Repeat revascularization 1.58 (1.28–1.96), Myocardial infarction 1.50 (1.18–1.89), MACE 1.47 (1.24 –1.74)
Sarno et al[44]	MACCEs in the 87% of the CR cohort at 24 months and 75% at 60 months. Definite stent thrombosis occurred in 2.6% of the IR cohort and 3.9% of the CR cohort (p =0.45), definite or probable stent thrombosis occurred in 6.5% in the IR cohort versus 8.6% in the CR cohort (p =0.41).
Sohn et al[20]	(CR versus IR) MACCE (34.7% vs. 45.1%; adjusted hazard ratio [HR], 0.65; 95% CI: 0.44-0.95, P = 0.03), all-cause death adjusted HR, 0.48; 95% CI, 0.29-0.80, P < 0.01).
Song et al[45]	(CR versus IR) MACE (HR 0.64; 95% CI 0.46–0.88; p=0.01) and revascularization (HR 0.61; 95% CI 0.42–0.90; p = 0.01) death (HR 0.87; 95% CI 0.48–1.57; p = 0.64) and MI (HR 0.62; 95% CI 0.23–1.67; p = 0.35). The rate of periprocedural MI and stent thrombosis was comparable in two cohorts (4.7% in the CR group vs. 3.6% in the IR group, p = 0.42; 1.6 vs. 1.3%, p = 0.72, respectively).
Srinivas et al[46]	(CR versus IR) mortality HR: 1.10 (95% CI: 0.58-2.10) and repeat revascularization HR:0.92 (0.66-1.29)
Tamburino et al[47]	(CR vs IR) primary composite endpoint HR:0.43 (0.29–0.63, P < 0.0001), cardiac death HR: 0.37 (0.15–0.92, P = 0.03),combination of cardiac death or MI HR:0.34 (0.16–0.75 P =0.008) and repeat revascularization HR:0.45 (0.29–0.69, P = 0.0003)
Valenti et al[48]	The survival rates were 91.6 and 87.4% in the CR and IR cohorts respectively (P = 0.025). CR was inversely proportional to mortality (HR 0.44; 95% CI 0.22–0.87; P = 0.021).
Van den Brand et al[31]	Outcomes Events/CR Total Events/IR Total Unplanned revascularization 34/406 61/170 Myocardial infarction 20/406 10/170 Death 7/406 6/170

Wu et al[5]	Death (HR=1.12; 95% CI, 1.01–1.26, P=0.04). 8-year survival was 78.5% and 80.8% for IR and CR (P=0.04). Mortality IR vs. CR (adjusted HR=1.16; 95% CI, 1.06–1.26, P=0.001).
Wu et al[49]	Among 6511 propensity-matched individuals (IR compared to CR) (79.3% vs. 81.4%, P=0.004), and death (HR=1.16, 95% CI: 1.06–1.27). 5-year survival rate (IR: 79.3% vs. CR: 81.4%, P=0.004)
Yang et al[50]	No differences in outcomes between the two cohorts at follow-up. Outcomes Events/CR Total Events/IR Total Repeat revascularization 4/99 17/255 MI 1/99 4/255 Death 3/99 7/255
George et al[51]	(CR versus IR) Mortality (adjusted HR: 0.70; 95% CI: 0.56 to 0.87; p = 0.002)
Hannan et al[52]	2.5-year Mortality Complete rev vs Complete rev for CTO, incomplete for ≥1 other lesions adjusted HR 1.11 (0.74, 1.68). 2.5-year Mortality Complete rev vs Incomplete rev for CTO adjusted HR 1.63 (1.28, 2.08) <0.0001
Danzi et al[53]	2-year cardiac death free survival was better the complete revascularization cohort compared to incomplete revascularization (96 vs 78 p = 0.002)
Chang et al[54]	IR with drug-eluting stents in multivessel disease was associated with increased MI risk (HR, 1.86; 95% CI, 1.08-3.19; P = 0.024) and similar risk of death (HR:1.03; 95% CI, 0.80-1.32; P = .83) compared to CR.

Table 4. Pooled OR and 95% CI for the studies included in the meta-analysis

Outcome	Subgroup analysis	OR	95% CI	I^2	P value
Death	All	0.69	0.61-0.78	77.03	<0.001
	Anatomic	0.69	0.61-0.79	80.60	<0.001
	Scored based	0.73	0.50-1.07	60.81	0.03
	CTO	0.65	0.53-0.80	68.13	<0.001
	Non CTO	0.71	0.61-0.82	78.6	<0.001
	ACS	0.71	0.44-1.11	0	0.95
Repeat revascularization	All	0.60	0.45-0.80	92.87	<0.001
	Anatomic	0.58	0.41-0.82	94.23	<0.001
	Scored based	0.64	0.54-0.76	0	0.59
Myocardial Infraction	All	0.63	0.50-0.79	62.4	<0.001
	Anatomic	0.60	0.45-0.81	65.86	0.07
	Scored based	0.64	0.51-0.79	0.00	0.72
MACE	All	0.66	0.51-0.85	93.29	<0.001
	Anatomic	0.64	0.46-0.89	94.5	<0.001
	Scored based	0.68	0.50-0.93	70.87	0.02
	ACS	0.79	0.54-1.17	81.86	0.02
Stent thrombosis	All	0.81	0.49-1.33	49.2	0.14

Figure 2: Risk of death with complete versus incomplete revascularization

Death

Study name	Odds ratio	Lower limit	Upper limit
Appleby et al32	0.53	0.47	0.60
Bourassa et al33	0.74	0.50	1.09
Breeman et al34	1.08	0.36	3.19
Chung et al35	0.44	0.29	0.68
Deligonul et al37	0.92	0.35	2.46
D'Oliveira Vieira et al36	0.59	0.29	1.21
Généreux et al6	0.43	0.28	0.66
Hambraeus et al13	0.51	0.45	0.58
Hannan et al.4	0.76	0.69	0.84
Hannan et al.38	0.65	0.54	0.78
Ijsselmuiden et al9	2.88	0.74	11.16
Kim et al39	0.67	0.44	1.02
Kip et al40	0.76	0.51	1.15
Kobayashi et al18	0.21	0.01	4.04
Kloeter et al41	3.60	0.86	15.00
Malkin et al22	3.10	1.71	5.63
Mariani et al72	0.64	0.03	13.49
Nikolsky et al42	0.37	0.17	0.81
Norwa-Otto et al43	0.93	0.64	1.36
Park et al17	0.57	0.37	0.89
Rosner et al8	0.70	0.44	1.12
Sarno et al44	0.62	0.30	1.26
Sohn et al20	0.49	0.27	0.87
Song et al45	0.75	0.43	1.28
Srinivas et al46	1.19	0.64	2.21
Tamburino et al47	0.33	0.13	0.82
Valenti et al48	0.33	0.18	0.61
Van den Brand et al31	0.48	0.16	1.45
Wu et al5	0.87	0.78	0.97
Wu et al49	0.83	0.75	0.91
Yang et al50	1.11	0.28	4.37
Malkin et al23	0.25	0.10	0.63
George et al51	0.70	0.56	0.87
Danzi et al53	0.08	0.01	0.72
Chang et al54	0.97	0.76	1.24
	0.69	0.61	0.78

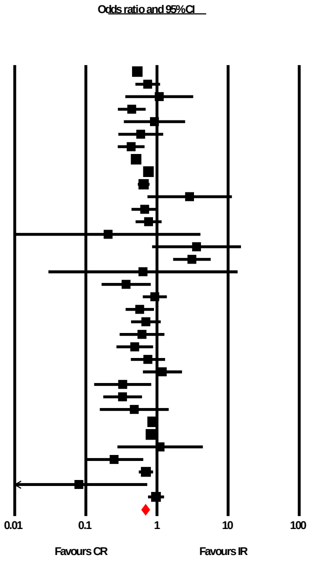


Figure 3: Risk of MACE with complete versus incomplete revascularization

MACE

Study name	Odds ratio	Lower limit	Upper limit
Chung et al35	0.82	0.59	1.13
Gao et al7	1.00	0.77	1.30
Généreux et al6	0.47	0.35	0.62
Hambraeus et al13	0.36	0.34	0.39
Ijsselmuiden et al9	0.76	0.43	1.37
Kim et al39	0.77	0.54	1.11
Park et al17	0.49	0.39	0.61
Rosner et al8	0.66	0.55	0.80
Sohn et al20	0.65	0.39	1.06
Song et al45	0.52	0.37	0.71
Tamburino et al47	0.38	0.26	0.58
Kobayashi et al18	1.44	0.68	3.04
Mariani et al72	0.98	0.74	1.29
Chang et al54	0.89	0.72	1.11
	0.66	0.51	0.85

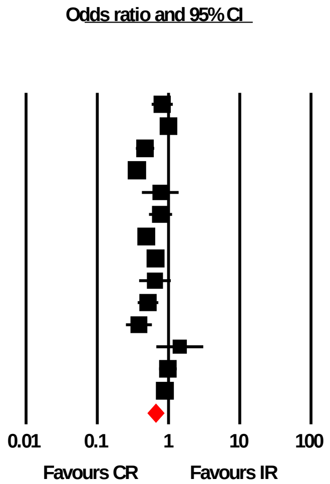


Figure 4: Risk of repeat revascularization with complete versus incomplete revascularization

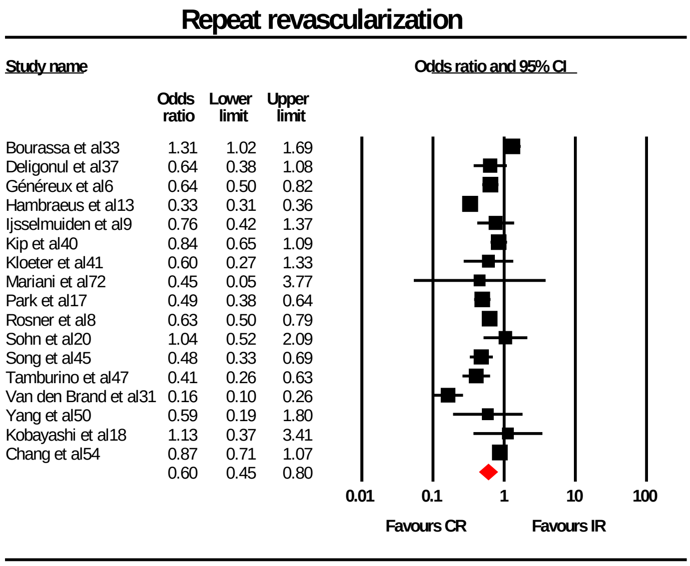


Figure 5: Risk of myocardial infraction with complete versus incomplete revascularization

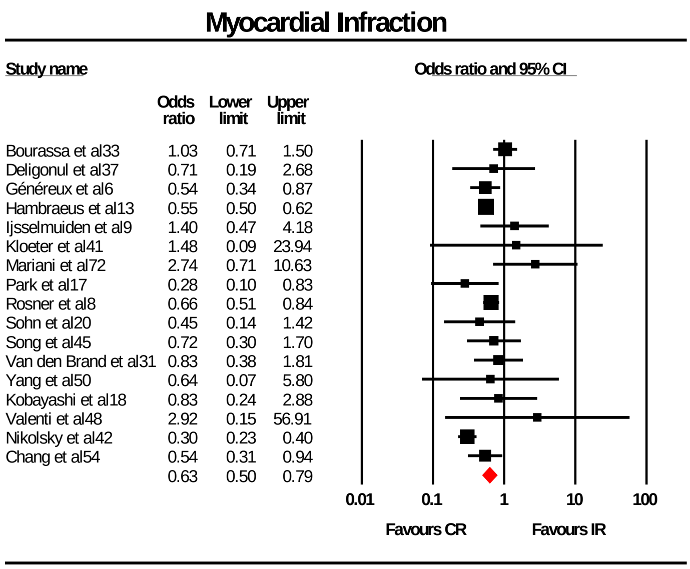
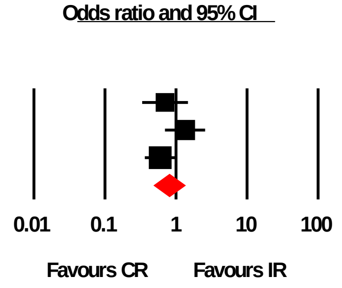


Figure 6: Risk of stent thrombosis with complete versus incomplete revascularization

Stent thrombosis

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Park et al	0.70	0.34	1.46	-0.95	0.34
Sarno et al	1.34	0.71	2.54	0.89	0.37
Généreux et al 2015	0.60	0.37	0.98	-2.06	0.04
	0.81	0.49	1.33	-0.85	0.40



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