EuroIntervention 2012;7:1095-1102 publish online ahead of print September 2011

Clinical outcomes based on completeness of revascularisation in patients undergoing percutaneous coronary intervention: a meta-analysis of multivessel coronary artery disease studies

Vikas Aggarwal[1], MD; Swapnil Rajpathak[2], MB, BS, PhD; Manjeet Singh[3], MD; Benjamin Romick[4], MD; Vankeepuram S. Srinivas[4]*, MB, BS, MS

1. Department of Medicine, Jacobi Medical Center, Bronx, NY, USA; 2. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA; 3. Department of Medicine, Bronx-Lebanon Hospital, Bronx, NY, USA; 4. Division of Cardiology, Department of Medicine, Montefiore Medical Center, Bronx, NY, USA

This paper also includes accompanying supplementary data published at the following website: www.eurointervention.org

KEYWORDS

- coronary artery disease
- angioplasty
- intermediate coronary lesions

Abstract

Aims: Most studies investigating completeness of revascularisation and outcomes for multivessel disease (MVD) patients are limited by small sample size.

Methods and results: We searched PUBMED, Cochrane and EMBASE for studies comparing outcomes of MVD patients with complete revascularisation (CR) vs. incomplete revascularisation (IR) in the stent era. We identified nine studies that met our selection criteria. Compared to IR, patients undergoing CR had significantly lower risk of mortality (relative risk (RR): 0.82; 95% confidence interval (CI): 0.68-0.99; p=0.05), non-fatal myocardial infarction (MI) (RR: 0.67; 95% CI: 0.53-0.84; p <0.01) and subsequent coronary artery bypass graft surgery (CABG) (RR: 0.70; 95% CI: 0.52-0.95; p=0.02) whereas no difference was noted in the incidence of repeat percutaneous coronary intervention (PCI) (RR: 0.87; 95% CI: 0.69-1.11; p=0.28). Average weighted follow up was approximately 29 months for mortality, subsequent CABG and Repeat PCI whereas it was 19 months for non-fatal MI. The results were similar after excluding the only RCT or the one study restricted to diabetics or the study restricted to drug-eluting stent use.

Conclusions: In patients with multivessel coronary disease, complete revascularisation with PCI may be associated with better outcomes than incomplete revascularisation.

* *Corresponding author: Division of Cardiology, Department of Medicine, Montefiore Medical Center, 1825, Eastchester Road, Suite W1-120, Bronx, NY, 10461, USA. E-mail: vsriniva@montefiore.org*

DOI: 10.4244/EIJV7I9A174

Introduction

Percutaneous coronary intervention (PCI), with the use of stents in general and drug eluting stents (DES) in particular, is an important revascularisation option that not only improves angina, but also reduces the need for subsequent revascularisation in patients with stable ischaemic coronary artery disease (CAD)[1,2]. In patients with multivessel disease (MVD), PCI operators often face a choice between seeking complete revascularisation (CR) of all haemodynamically significant lesions or a selective strategy often termed incomplete revascularisation (IR). As opposed to coronary artery bypass graft surgery (CABG) where CR is more often achieved[3], CR with PCI is not attempted in the majority of patients for several reasons including: presence of serious medical conditions, one or more chronic total occlusions (CTO), left ventricular dysfunction or simply because in the opinion of the operator, treatment of selected lesions and vessels is considered adequate for relief of patients symptoms[4]. Although several randomised and non-randomised studies have compared PCI to CABG and/or medical therapy in MVD[5-8], only a few have examined the effect of completeness of revascularisation, often with variable results[4,9-16]. Some studies have reported better outcomes in patients receiving CR with PCI compared to IR[10,14], whereas others have demonstrated no significant differences in outcomes[4,13]. Therefore choice of CR versus IR with PCI for MVD remains a matter of debate. To our knowledge, there has been no systematic review summarising the literature based on completeness of revascularisation to assist in appropriate decision-making in patients with MVD undergoing PCI. In addition, since most studies investigating the completeness of revascularisation with PCI are individually limited by small sample size to detect differences in mortality and recurrent myocardial infarction (MI)[11,15,16], we performed a meta-analysis to evaluate the effect of completeness of revascularisation with PCI on subsequent clinical outcomes.

Methods

We based our methods on the widely accepted (MOOSE checklist) guidelines for reporting meta-analysis of observational studies[17].

SEARCH STRATEGY AND STUDY SELECTION

We searched PUBMED, Cochrane and EMBASE for studies using the key words "Percutaneous coronary intervention", "Angioplasty", "multi-vessel" and "multivessel", "multi vessel", "PCI", "PTCA", "PCA", "PCIA", and "MVD". We limited our search to studies in human subjects in peer reviewed journals until July 31, 2009 and in addition checked the reference lists of reviewed articles, editorials and original studies identified by the electronic search to find other potentially eligible studies. Two authors (V.A. and M.S.) independently selected the studies to be included in this analysis; discrepancies were resolved by a third reviewer (V.S.S.). The following criteria were used for study selection: 1) study population consisting of subjects with MVD disease not restricted to acute MI. 2) PCI with stents (if indicated) being the revascularisation modality of choice. 3) publication in a peer reviewed journal.

STUDY QUALITY ASSESSMENT

Study quality was assessed using the internal validity criteria of the US Preventive Services Task Force[18], assigning a rating of "good" when all criteria were met; "fair" when one criterion was not met and "poor" if more than one criterion were not met. The specific criteria for this assessment were: 1) MVD definition based on presence of >50% diameter stenosis in >2 major epicardial vessels; 2) CR defined as no remaining lesion >50% stenosis after PCI; 3) subjects with prior revascularisation were excluded; 4) similar follow-up for both the comparison groups; 5) well defined individual outcomes. All nine selected studies met at least four of the five criteria and were judged to be either good or fair. Differences with regard to study quality or in any of the extracted data were resolved by re-examining the studies with a third observer (V.S.S.) and by consensus.

DATA ABSTRACTION

Two authors (V.A. and M.S.) independently abstracted data from the selected studies. All reported baseline characteristics were extracted from each of the included studies. Further, we extracted the incidence rates for the following clinical outcomes: all-cause mortality, non-fatal MI, subsequent CABG, repeat PCI in both CR and IR groups as these outcomes were reported by most of the included studies. **Appendix 1** summarises the definitions for non-fatal MI used by all included studies. Repeat PCI did not include PCI performed as a staged procedure in any of the included studies. When available, adjusted hazard ratio (HR) was also extracted for all the outcomes.

DATA SYNTHESIS

Treatment effect for each outcome was assessed as a relative risk (RR) with 95% confidence interval (CI). RR was defined as the risk of experiencing the outcome among those achieving CR compared with those achieving IR. Adjusted HR was used to estimate RR when available. The summary RR was estimated using the DerSimonian and Laird method for random effects[19]. The random-effects model is reported in the text and figures. To assess heterogeneity across studies, we used the Cochran Q statistic based on the pooled RR by Mantel-Haenszel and measured inconsistency (I^2; the percentage of total variance across studies attributable to heterogeneity rather than chance) of treatment effects across studies[20]. Publication bias (i.e., the likelihood of small yet nominally significant studies being selectively published in the literature) was appraised by means of visual inspection of funnel plots[21] and using the methods of Egger et al[22]. All p values were two tailed, and $p < 0.05$ was considered statistically significant. All analyses were performed using STATA software, version 11.0 (STATA, College Station, TX, USA) and Comprehensive Meta-analysis software, version 2 (Biostat, Englewood, NJ, USA).

Results

SEARCH RESULTS AND STUDY SELECTION

Among the 1,634 studies initially screened, 48 met the criteria for a full text review out of which nine were deemed to be suitable for a study quality assessment. All nine studies were deemed to be

either good or fair based on previously mentioned study quality assessment criteria and were included in the meta-analysis **(Figure 1)**.

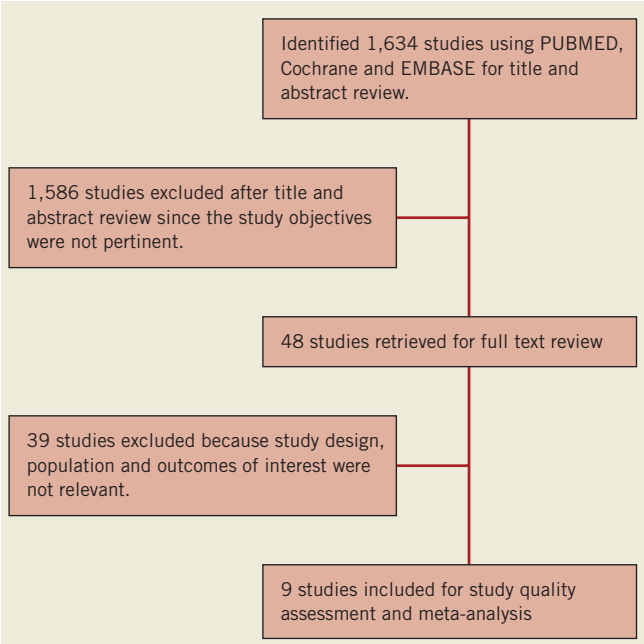


Figure 1. *Flowchart of selection of studies for inclusion in the meta-analysis.*

STUDY AND PATIENT CHARACTERISTICS

Important study characteristics are illustrated in the **Table 1** and baseline patient characteristics for all studies are summarised in **Table 2**. Out of the nine selected studies, one was a randomised clinical trial (RCT)[16] and the other eight were observational cohort studies[4,9-15]. Together, these studies included a total of 37,116 patients with MVD who received either CR (n=11,596) or IR (n=25,520). All included studies defined CR as no remaining lesions >50% in any of the major epicardial vessels. None of them used functional criteria for defining completeness of revascularisation. One study only included patients with diabetes mellitus (DM)[12], one restricted itself to DES use[14] and one only had patients with unstable angina[15]. There was no evidence for a publication bias in these analyses **(Appendices 2-6)**.

ALL-CAUSE MORTALITY

Compared to IR, patients undergoing CR had significantly lower risk of mortality (RR: 0.82; 95% CI: 0.68-0.99; p=0.05) during an average (weighted mean) follow up of 29.4 months **(Figure 2)**. There was no significant heterogeneity observed across these studies (Q statistic=11.0, p=0.14, I^2=36.1%). The results were similar after excluding the only RCT[16] (RR 0.82; 95% CI: 0.71-0.95; p <0.01) or when the study restricted to patients with DM alone[12] was excluded (RR: 0.85; 95% CI 0.77-0.94; p <0.01).

NON-FATAL MI

Compared to IR, patients undergoing CR had significantly lower risk of non-fatal MI (RR: 0.67; 95% CI: 0.53-0.84; p <0.01) during an average (weighted mean) follow-up of 19.8 months **(Figure 3)**. There was no significant heterogeneity observed across these studies (Q statistic=6.7, p=0.46, I^2=0.0%). The results were similar to the overall results after excluding the only RCT[16] (RR: 0.64; 95% CI: 0.50-0.80; p <0.01), when the study restricted to patients with DM alone was excluded[12] (RR: 0.71; 95% CI : 0.56-0.91; p <0.01) or when the study restricted to DES use[14] was excluded (RR: 0.68; 95% CI : 0.52-0.88; p <0.01).

SUBSEQUENT CABG

Compared to IR, patients undergoing CR had significantly lower risk for undergoing subsequent CABG (RR: 0.70; 95% CI: 0.52-0.95; p=0.02) during an average (weighted mean) follow-up of 29.1 months **(Figure 4)**. There was significant heterogeneity observed

Table 1. Important characteristics for all the studies included in the meta-analysis.

Study, year	Study design (Setting)	Study population	Stent type	Sample size (CR/IR)	Mean follow-up (months)
Kloeter, 2001	Single centre cohort (Europe)	All patients receiving PCI	BMS	101/149	32
Mariani, 2001	Multicentre cohort (Italy)	Unstable angina only	BMS	44/147	12
van den Brand, 2002	Multicentre cohort of RCT (North America/ Europe/ Australia/ South America)	All patients receiving PCI	BMS	406/170	12
Ijsselmuiden, 2004	Randomised clinical trial (Netherlands)	Stable angina only	BMS	108/111	55
Nikolsky, 2004	Single centre cohort (Europe)	All Diabetics receiving PCI	BMS	94/258	60
Hannan, 2006	Multicentre cohort (United States)	All patients receiving PCI	BMS	6817/15128	36
Srinivas, 2007	Multicentre cohort (United States/ Canada)	All patients receiving PCI	BMS	315/1466	12
Tamburino, 2008	Single centre cohort (Italy)	All patients receiving PCI	DES	212/296	27
Hannan, 2009	Multicentre cohort (United States)	All patients receiving PCI	Both	3499/7795	19

PCI: percutaneous coronary intervention; BMS: bare metal stent; DES: drug eluting stent; RCT: randomised controlled trial

Table 2. Baseline comparison of patient characteristics in individual studies by revascularisation type.

	Mariani, 2001		Hannan, 2009		Nikolsky, 2004		Kloeter, 2001		van den Brand, 2002		Tamburino, 2008		Srinivas, 2007		Ijsselmuiden, 2004		Hannan, 2006	
	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR
Sample size*	49	158	3499	7795	94	258	101	149	108	111	212	296	315	1466	108	111	6817	15128
Mean age (years)	63.7	63.9			62	62	57	61	62	61.7	61	63	61.9	64.1	62	61.7		
Age <60 years (%)			34.5	31.1													37.3	32.4
Female sex (%)	26.5	17	33.2	32.9	27.8	26.9	17	18	24	26	21	21	28.6	34.5	24	26	31	32
Caucasian race (%)			79.4	71.7									78.4	78.5			88.1	86.4
Prior MI (%)	37	47	28.8	37.6	27.3	37.1	63	57	41	44	23	33	20.6	32.9	41	44	26.3	27.5
Hypertension (%)					49.2	45.4	47	50	32	37	55	67	67.2	68.9	32	37		
Hypercholesterolaemia (%)					60.2	57.9	68	65	56	45	55	60	63.8	64.6	56	45		
Smoking (%)					17.3	15.9	39	28	31	32	35	34	63.4	65.7	31	32		
Diabetes mellitus (%)	26	14.5	28.3	34.3	100	100	8	20	11	17	32	35	29.8	33.3	11	17	23.5	26.4
Cerebrovascular disease (%)			7.3	8.2							4	5	6.7	6.0			2.6	3.9
Peripheral arterial disease (%)			5.1	8.3							7	6	6.7	7.6			4.2	7.6
Chronic obstructive lung disease (%)			6.1	6.8							6	6					4.6	6.3
> 1 CTO (%)	14	41	0	35.2			21	31	5.4	19.4	23	51	21	31.6			0	30.1
Three-vessel disease (%)	45	51	9.9	31.6	41.9	50	15	24	3	9	15	54	11.7	36.5	3	9	6.9	25.1
Mean EF							64	61			51	49	54.3	55.1				
EF <40%	0	11	7.7	12.6	12.6	18.6					11	18					8.1	14.4
Stent implantation (%)	84	83	16.5	6.1			29	25			100	100	90.5	83.1				
DES only (%)	0	0	75.5	80.2	0	0	0	0	0	0	100	100	0	0	0	0	0	0

DES: drug eluting stent; EF: ejection fraction; CTO: chronic total occlusion; MI: myocardial infarction; CR: complete revascularisation; IR: incomplete revascularisation

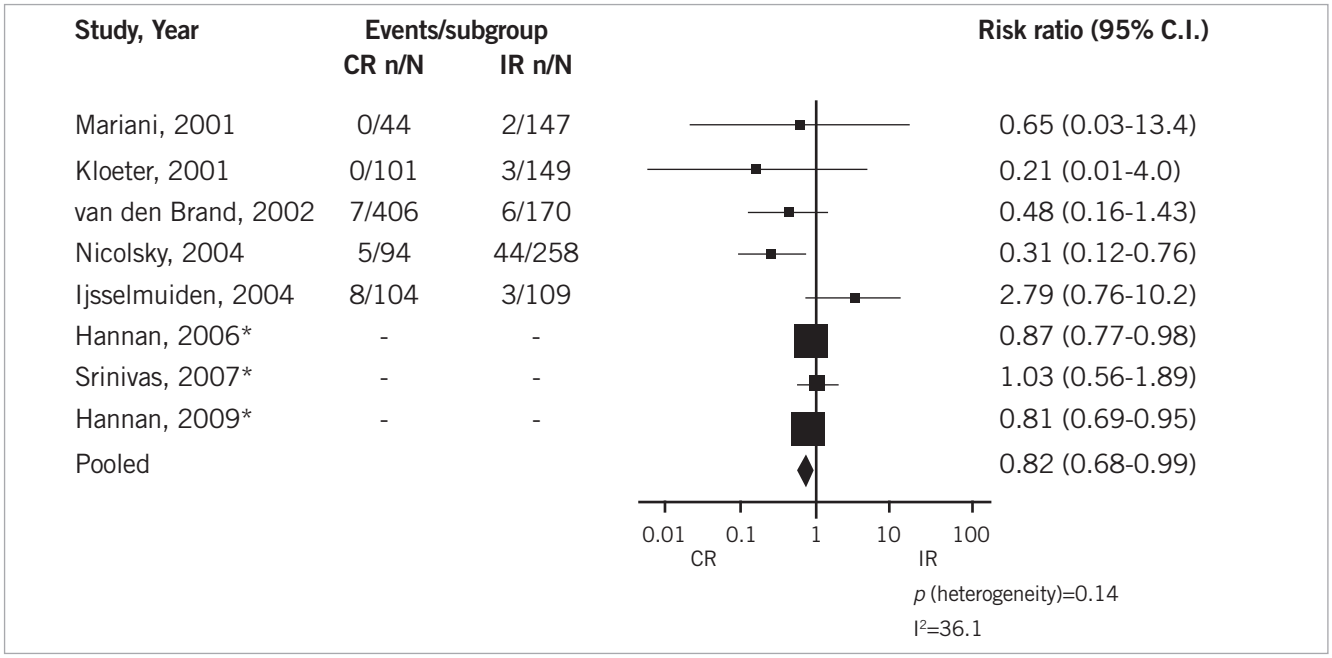


Figure 2. *Pooled analysis with risk ratios and related 95% CI's for the occurrence of all-cause mortality. *Adjusted hazard ratio was used as an estimate of risk ratio. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI's. The size of the box is proportional to the weight of the study in the pooled analysis. Diamonds represent pooled random-effect estimates (risk of experiencing the outcome among those achieving CR compared with those achieving IR). The vertical line at 1.0 indicates no effect of completeness of revascularisation on the risk of experiencing the outcome. CR: complete revascularisation; IR: incomplete revascularisation; CI: confidence interval*

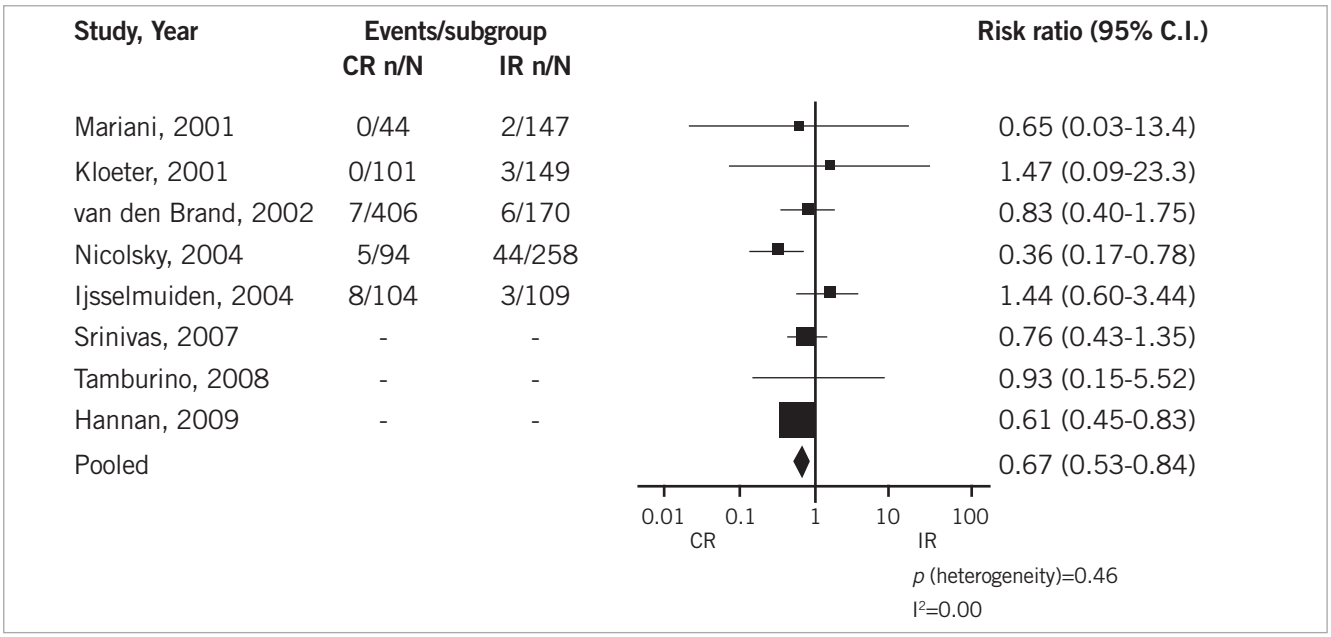


Figure 3. *Pooled analysis with risk ratios and related 95% CI for the occurrence of non-fatal MI. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI's. The size of the box is proportional to the weight of the study in the pooled analysis. Diamonds represent pooled random-effect estimates (risk of experiencing the outcome among those achieving CR compared with those achieving IR). The vertical line at 1.0 indicates no effect of completeness of revascularisation on the risk of experiencing the outcome. CR: complete revascularisation; IR: incomplete revascularisation; CI: confidence interval; MI: myocardial infarction*

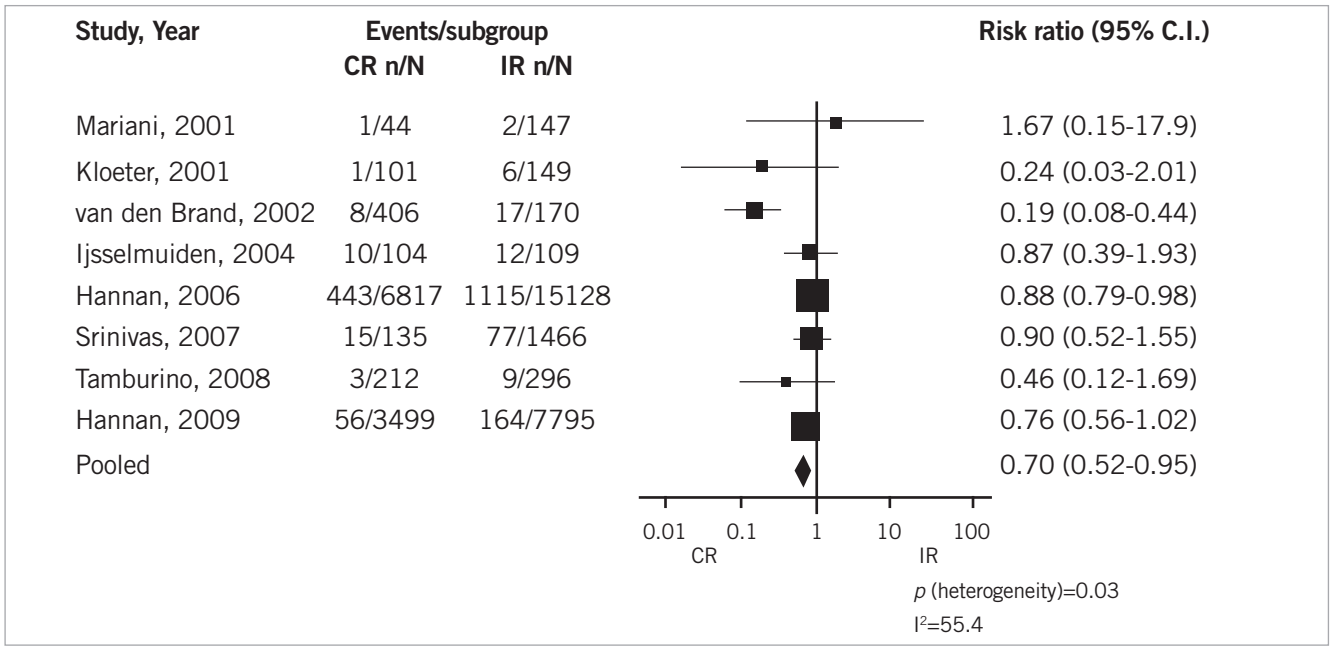


Figure 4. *Pooled analysis with risk ratios and related 95% CI for the occurrence of subsequent CABG. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CIs. The size of the box is proportional to the weight of the study in the pooled analysis. Diamonds represent pooled random-effect estimates (risk of experiencing the outcome among those achieving CR compared with those achieving IR). The vertical line at 1.0 indicates no effect of completeness of revascularisation on the risk of experiencing the outcome. CR: complete revascularisation; IR: incomplete revascularisation; CI: confidence interval; CABG: coronary artery bypass graft surgery*

across these studies (Q statistic=15.7, p=0.03, I^2=55.4%). Whereas, excluding the study by van den Brand et al[13] eliminated the heterogeneity (Q statistic=3.4, p=0.76, I^2=0.0%), the results remained similar for CR vs. IR (RR: 0.86; 95% CI: 0.78-0.95; p <0.01). In sensitivity analysis, the RR was similar to the overall results both after excluding the only RCT[16] (RR: 0.68; 95% CI: 0.48-0.95;

p=0.03) and on excluding the study restricted to DES use[14] was excluded (RR: 95% CI: 0.52-0.98; p=0.04).

REPEAT PCI

Repeat PCI rates were similar in both groups (CR and IR) (RR: 0.87; 95% CI: 0.69-1.11; p=0.28) during an average (weighted mean) follow-up of 29.1 months **(Figure 5)**. There was significant heterogeneity across these studies (Q statistic=72.6, p<0.01, I2=90.4%). Excluding the van den Brand et al[13] and Tamburino et al[14] studies eliminated the heterogeneity (Q statistic=10.1, p=0.07, I^2=50.5%) but the results were similar to the overall analysis (RR: 1.04; 95% CI: 0.84-1.29; p=0.72). In sensitivity analysis, the RR was similar to the overall results both after excluding the only RCT[16] (RR: 0.90; 95% CI: 0.70-1.16; p=0.449) or when the study restricted to DES use[14] was excluded (RR: 0.95; 95% CI: 0.74-1.21; p=0.69).

Discussion

The results of this meta-analysis clearly demonstrate the lack of well powered randomised studies looking at completeness of revascularisation and long-term outcomes. However, based on existing reports we observed that patients receiving complete revascularisation with PCI experience better clinical outcomes than those receiving incomplete revascularisation. To our knowledge, this is the first report in the literature of pooled analysis of existing evidence that compares complete with incomplete revascularisation.

Multiple surgical series have reported better long-term outcomes for patients receiving CABG with complete revascularisation[13,23-25]. However, individual studies that compare outcomes for CR versus IR have yielded mixed results with PCI[10,12,15,16]. Overall, our systematic review included only nine studies comparing IR vs. CR that fulfilled stringent criteria and all except one were either registries or a cohort within a RCT[13]. The only randomised comparison[16] was underpowered to detect a difference in individual outcomes and did not show any difference in outcomes between IR and CR groups. While randomised control trials are desirable, meta-analyses based on observational data are commonly reported in literature, including the coronary revascularisation literature[5] and at the moment we only have observational data as a guide to clinical decision making on this issue of completeness of revascularisation with PCI. In our meta-analysis, patients who received CR had a marginally lower risk of death, MI and subsequent CABG compared to patients receiving IR, although the risk of repeat PCI was not significantly different. A natural question that follows is why patients with CR experience lower risk of death or non-fatal MI. One possible explanation is that CR somehow protects against clinical events. However, an alternative explanation is that patients receiving CR had better clinical risk profile than those receiving IR. In fact, in almost all the studies in this meta-analysis, patients receiving CR had lower incidence of clinical comorbidities, had better ejection fractions, had fewer CTO's attempted and more often had two-vessel disease rather than three-vessel disease compared to IR patients

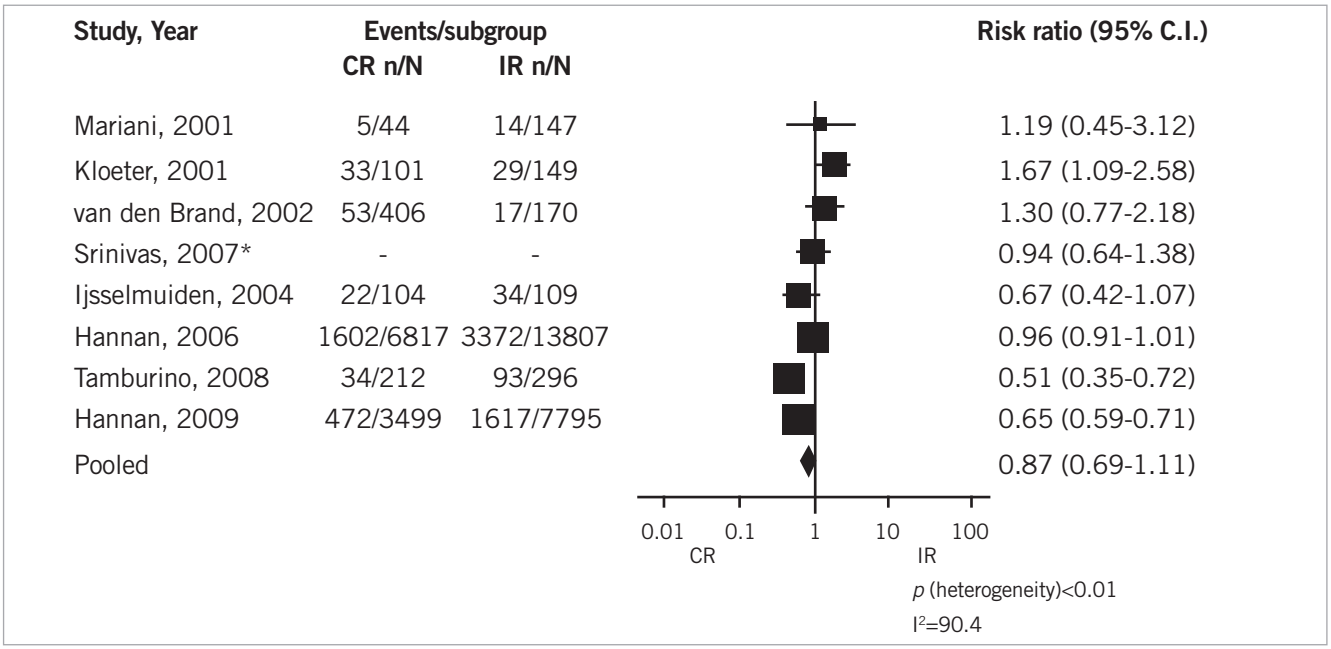


Figure 5. *Pooled analysis with risk ratios and related 95% CI for the occurrence of repeat PCI. *Adjusted hazard ratio was used as an estimate of risk ratio. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI's. The size of the box is proportional to the weight of the study in the pooled analysis. Diamonds represent pooled random-effect estimates (risk of experiencing the outcome among those achieving CR compared with those achieving IR). The vertical line at 1.0 indicates no effect of completeness of revascularisation on the risk of experiencing the outcome. CR: complete revascularisation; IR: incomplete revascularisation; CI: confidence interval; PCI: percutaneous coronary intervention*

(Table 2). Although we used risk-adjusted point estimates whenever available, residual confounding cannot be entirely discounted. Nonetheless, the observation that CR is associated with a lower incidence of subsequent death and non-fatal MI is novel and bears consideration. Similarly, the effect of CR on reducing the frequency of subsequent CABG is not surprising and has been observed in multiple individual studies[4,9-14,16]. However, the absence of significant differences in subsequent PCI rates is likely to be related to several possible factors. To begin with, repeat PCI in patients with MVD is a result of either restenosis or plaque progression. Except for two studies[10,14], BMS was used predominantly in all the rest, likely resulting in higher need of repeat revascularisation than would have resulted if DES had been used. Furthermore, recent evidence also indicates that a significant proportion of patients with MVD have progression requiring subsequent revascularisation within five years of initial PCI[26,27]. Therefore, the presence of these competing risks of higher restenosis rates from BMS use and plaque progression possibly resulted in the lack of difference in repeat PCI rates between CR and IR.

The implications of these results are that for patients with MVD, the achievement of CR, whenever possible, ought to be the goal of revascularisation. All studies in this meta-analysis used anatomic criteria to guide revascularisation choice; current evidence suggests that a functional testing strategy may be superior. Although non-invasive stress imaging studies are limited in their ability to accurately localise ischaemia-producing lesions particularly in MVD[28], results from the FAME study support the use of physiologic techniques such as fractional flow reserve measurement to ascertain lesions requiring revascularisation[29].

Currently there are several effective therapies for patients with MVD including medical therapy, PCI and CABG. Therefore, the current challenge facing practitioners is that of choosing the optimal therapy or combination of therapies to achieve the best possible outcome. Although completeness of revascularisation may not be the primary consideration when determining suitable options, the results of our analysis seems to suggest otherwise. Therefore, practitioners need to carefully consider the optimal modality to achieve complete relief of ischaemia in patients with MVD. For some it may mean the judicious use of DES, whereas in others, for whom CR may not be achievable with PCI, CABG may be an appropriate alternative.

However, these results should be interpreted with some degree of caution and are only hypotheses generating, since the choice of CR versus IR was not random in eight out of nine studies. As a result, the differences in outcome may reflect the underlying differences in clinical characteristics rather than the result of completeness of revascularisation. Albeit, individual studies did compare baseline characteristics and adjusted for confounding wherever indicated and we used adjusted hazard ratios to estimate our pooled estimates whenever reported, nonetheless residual confounding can still be present. This meta-analysis included studies from United States, European and Canadian centres diversifying the patient population, but these results are largely driven by the reports from the New York State PCI reporting system[9,10] and the Dynamic registry[4] which have their inherent limitations[30]. Although we used standard meta-analytic techniques for pooled analysis, there were substantial variations in the quality of data based on the outcome variable. As a result, although the tests for heterogeneity were not significant for the pooled analyses of death and MI, significant heterogeneity was observed for subsequent CABG and PCI, limiting the accuracy of the pooled estimate for these latter endpoints. Lastly, since we excluded studies of culprit only versus complete revascularisation in the setting of AMI, the results of this analysis may not be applicable to such clinical scenarios.

In conclusion, the results of our meta-analysis demonstrate the lack of well powered randomised studies comparing clinical outcomes in patients undergoing elective PCI by completeness of revascularisation and suggest that complete revascularisation with PCI is associated with better clinical outcomes than incomplete revascularisation. These results are only hypothesis generating and further investigation with larger randomised controlled trials is warranted to address this issue.

Acknowledgements

We sincerely thank Racheline Haboush, Jennifer Shangkuan and Atul Limaye for their help in study search and selection.

Conflict of interest statement

The authors have no conflict of interest to declare.

References

1. Hilliard AA, From AM, Lennon RJ, Singh M, Lerman A, Gersh BJ, Holmes DR, Jr., Rihal CS, Prasad A. Percutaneous revascularization for stable coronary artery disease temporal trends and impact of drug-eluting stents. *JACC Cardiovasc Interv* 2010;3:172-9.

2. Prasad A, Rihal C, Holmes DR, Jr. The COURAGE trial in perspective. *Catheter Cardiovasc Interv* 2008;72:54-9.

3. Whitlow PL, Dimas AP, Bashore TM, Califf RM, Bourassa MG, Chaitman BR, Rosen AD, Kip KE, Stadius ML, Alderman EL. Relationship of extent of revascularization with angina at one year in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 1999;34:1750-9.

4. Srinivas VS, Selzer F, Wilensky RL, Holmes DR, Cohen HA, Monrad ES, Jacobs AK, Kelsey SF, Williams DO, Kip KE. Completeness of revascularization for multivessel coronary artery disease and its effect on one-year outcome: a report from the NHLBI Dynamic Registry. *J Interv Cardiol* 2007;20:373-80.

5. Benedetto U, Melina G, Angeloni E, Refice S, Roscitano A, Fiorani B, Di Nucci GD, Sinatra R. Coronary artery bypass grafting versus drug-eluting stents in multivessel coronary disease. A meta-analysis on 24,268 patients. *Eur J Cardiothorac Surg* 2009;36:611-5.

6. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic review: the comparative effectiveness of

percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med* 2007;147:703-16.

7. Caines AE, Massad MG, Kpodonu J, Rebeiz AG, Evans A, Geha AS. Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention and medical therapy for multivessel disease with and without left ventricular dysfunction. *Cardiology* 2004;101:21-8.

8. Varani E, Balducelli M, Vecchi G, Aquilina M, Maresta A. Comparison of multiple drug-eluting stent percutaneous coronary intervention and surgical revascularization in patients with multivessel coronary artery disease: one-year clinical results and total treatment costs. *J Invasive Cardiol* 2007;19:469-75.

9. Hannan EL, Racz M, Holmes DR, King SB, 3rd, Walford G, Ambrose JA, Sharma S, Katz S, Clark LT, Jones RH. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 2006;113:2406-12.

10. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S, King SB, 3rd. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv* 2009;2:17-25.

11. Kloeter UC, Jander NG, Buser PT, Osswald S, Mueller-Brand J, Pfisterer ME. Long-term outcome of angioplasty for multivessel coronary disease: importance and price of complete revascularization. *Int J Cardiol* 2001;79:197-205.

12. Nikolsky E, Gruberg L, Patil CV, Roguin A, Kapeliovich M, Petcherski S, Boulos M, Grenadier E, Amikam S, Linn S, Markiewicz W, Beyar R. Percutaneous coronary interventions in diabetic patients: is complete revascularization important? *J Invasive Cardiol* 2004;16:102-6.

13. van den Brand MJ, Rensing BJ, Morel MA, Foley DP, de Valk V, Breeman A, Suryapranata H, Haalebos MM, Wijns W, Wellens F, Balcon R, Magee P, Ribeiro E, Buffolo E, Unger F, Serruys PW. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. *J Am Coll Cardiol* 2002;39:559-64.

14. Tamburino C, Angiolillo DJ, Capranzano P, Dimopoulos K, La Manna A, Barbagallo R, Tagliareni F, Mangiafico S, Guzman LA, Galassi AR, Bass TA. Complete versus incomplete revascularization in patients with multivessel disease undergoing percutaneous coronary intervention with drug-eluting stents. *Catheter Cardiovasc Interv* 2008;72:448-56.

15. Mariani G, De Servi S, Dellavalle A, Repetto S, Chierchia S, D'Urbano M, Repetto A, Klersy C. Complete or incomplete percutaneous coronary revascularization in patients with unstable angina in stent era: Are early and one-year results different? *Catheter Cardiovasc Interv* 2001;54:448-53.

16. Ijsselmuiden AJ, Ezechiels J, Westendorp IC, Tijssen JG, Kiemeneij F, Slagboom T, van der Wieken R, Tangelder G, Serruys PW, Laarman G. Complete versus culprit vessel percutaneous coronary intervention in multivessel disease: a randomized comparison. *Am Heart J* 2004;148:467-74.

17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

18. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20:21-35.

19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

21. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

23. Gum PA, O'Keefe JH, Jr., Borkon AM, Spertus JA, Bateman TM, McGraw JP, Sherwani K, Vacek J, McCallister BD. Bypass surgery versus coronary angioplasty for revascularization of treated diabetic patients. *Circulation* 1997;96:II-7-10.

24. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularization Investigation. *Circulation* 1996;93:847.

25. Jones EL, Weintraub WS. The importance of completeness of revascularization during long-term follow-up after coronary artery operations. *J Thorac Cardiovasc Surg* 1996;112:227-37.

26. Chacko R, Mulhearn M, Novack V, Novack L, Mauri L, Cohen SA, Moses J, Leon MB, Cutlip DE. Impact of target lesion and nontarget lesion cardiac events on 5-year clinical outcomes after sirolimus-eluting or bare-metal stenting. *JACC Cardiovasc Interv* 2009;2:498-503.

27. Glaser R, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, Detre KM, Wilensky RL. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation* 2005;111:143-9.

28. Melikian N, De Bondt P, Tonino P, De Winter O, Wyffels E, Bartunek J, Heyndrickx GR, Fearon WF, Pijls NH, Wijns W, De Bruyne B. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv* 2010;3:307-14.

29. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.

30. Teirstein PS. The dueling hazards of incomplete revascularization and incomplete data. *Circulation* 2006;113:2380-2.

EuroIntervention 2012;7 publish online ahead of print September 2011

Online appendices

Appendix 1. Definition of non-fatal myocardial infarction in individual studies.

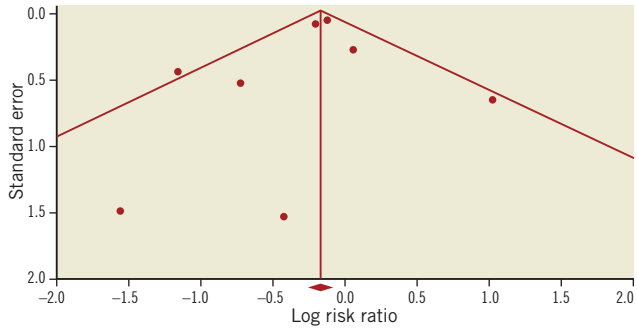
Study name	Definition of non-fatal myocardial infarction
Mariani, 2001	Elevation in creatine kinase more than twice the upper limit of normal.
van den Brand, 2002	New abnormal Q-waves and either a ratio of serum creatine kinase-MB isoenzyme to total creatine kinase that was greater than 0.1 or a creatine kinase-MB value that was five times the upper limit of normal.
Nikolsky, 2004	Elevation in creatine kinase more than twice the upper limit of normal.
Ijsselmuiden, 2004	Prolonged chest pain associated with either new Q-waves on the electrocardiogram or a rise in creatine kinase >200 U/L or in its MB fraction >20 U/L.
Srinivas, 2007	Evidence of two or more of the following: (1) clinical symptoms; (2) electrocardiogram evidence of myocardial ischaemia; (3) elevation of creatine kinase -MB >5% of total creatine kinase, total creatine kinase >2 times normal, lactic dehydrogenase-I > lactic dehydrogenase–II, or troponin > 0.2 ng/ml; and (4) new wall motion abnormalities.
Tamburino, 2008	Occurrence of ischaemic symptoms in the presence of electrocardiogram changes and rise of biochemical markers of myocardial necrosis.
Hannan, 2009	Subjects with myocardial infarction were identified using ICD code for myocardial infarction.

Appendix 2. Publication bias assessment using Egger's test.

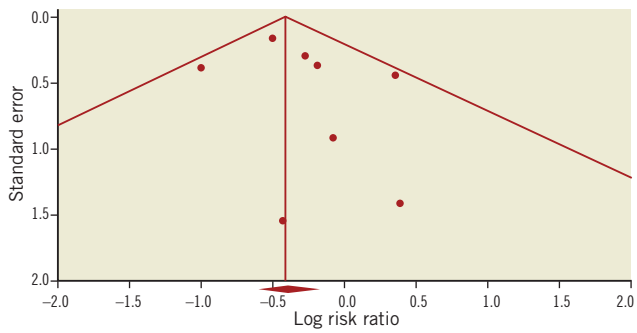
Outcome	*p* value
All-cause mortality	0.57
Non-fatal MI	0.38
Subsequent CABG	0.17
Repeat PCI	0.84

MI: myocardial infarction; CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention

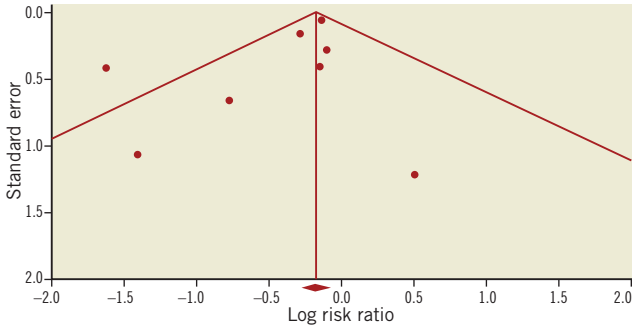
Appendix 3. Publication bias assessment via funnel plot for all-cause mortality. (Figure 6)



Appendix 4. Publication bias assessment via funnel plot for non-fatal myocardial infarction. (Figure 7)



Appendix 5. Publication bias assessment via funnel plot for subsequent coronary artery bypass graft surgery. (Figure 8)



Appendix 6. Publication bias assessment via funnel plot for repeat percutaneous coronary intervention. (Figure 9)