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Outcomes after Complete versus Incomplete Revascularization of Patients with Multivessel Coronary Artery Disease: A Meta-Analysis of 89,883 Patients Enrolled in Randomized Clinical Trials and Observational Studies

Short title: Completeness of revascularization and outcomes

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Abstract:
Objectives To perform a systematic review and meta-analysis of studies comparing complete revascularization (CR) vs. incomplete revascularization (IR) in patients with multivessel coronary artery disease (CAD).
Background There is conflicting data regarding the benefits of CR in patients with multivessel CAD.
Methods We identified observational studies and subgroup analysis of randomized clinical trials (RCTs) published in PUBMED from 1970 through September 2012 using the following keywords: percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), complete revascularization, and incomplete revascularization. Main outcome measures were total mortality, myocardial infarction and repeat revascularization procedures.
Results We identified 35 studies including 89,883 patients, of whom 45,417 (50.5%) received CR and 44,466 (49.5%) received IR. IR was more common after PCI than CABG (56% vs. 25%, p<0.001). Relative to IR, CR was associated with lower long-term mortality (risk ratio [RR]: 0.71; 95% confidence interval [CI]: 0.65-0.77, p<0.001), myocardial infarction (RR: 0.78; 95% CI: 0.68-0.90, p=0.001) and repeat coronary revascularization (RR: 0.74; 95% CI: 0.65-0.83, p <0.001). The mortality benefit associated with CR was consistent across studies irrespective of revascularization modality (CABG: RR: 0.70; 95% CI: 0.61-0.80, p<0.001 and PCI: RR: 0.72; 95% CI: 0.64-0.81, p<0.001) and definition of CR (anatomical definition: RR: 0.73; 95% CI: 0.67-0.79, p<0.001 and non-anatomical definition: RR: 0.57; 95% CI: 0.36-0.89, p=0.014).
Conclusions CR is achieved more commonly with CABG than PCI. Among patients with multivessel CAD, CR may be the optimal revascularization strategy.

Key words: Coronary artery disease, complete revascularization, percutaneous coronary intervention, coronary artery bypass surgery, meta-analysis

Over 1,000,000 coronary revascularization procedures are performed every year in the U.S. for the treatment of coronary artery disease (CAD) (1). Coronary revascularization improves symptoms and, in select groups, reduces myocardial infarction and long-term mortality (2-5). Achieving complete revascularization (CR) has long been a goal of coronary artery bypass graft (CABG) surgery (6-7). A seminal observation from the Coronary Artery Surgery Study (CASS) registry showed that patients with multivessel CAD and severe angina that received 3 or more grafts had better survival relative to patients that received 1 or 2 grafts (8). By extension, the concept of CR has also been advocated in percutaneous coronary intervention (PCI) (9-10). Despite this long-held belief observational studies have yielded conflicting results (10, 11-12) and no large multicenter randomized clinical trial (RCT) has ever tested whether CR is superior to incomplete revascularization (IR). CR is infrequent in clinical practice (10, 13) and guidelines do not formally address the issue of CR in detail (14-15). Thus, the purpose of the present investigation was to perform a systematic review and meta-analysis of RCTs and observational studies to determine if CR is associated with improved clinical outcomes compared to IR.

Methods We identified observational studies and RCTs published in PUBMED from 1970 through September 2012 using the following keywords: percutaneous coronary intervention, coronary artery bypass graft, complete revascularization, and incomplete revascularization. We limited our search criteria to include studies published in the English language and those involving humans. We identified additional studies by searching www.clinicaltrials.gov, by hand searching references cited in relevant publications. This methodological approach has been previously validated (16). The term RCT, as used throughout the manuscript, refers to the design of the study from which the data was obtained. It does not imply that the randomization variable was completeness of revascularization.

Data sources and study search strategy We included observational studies and RCTs that: 1) enrolled patients with multivessel CAD referred for coronary revascularization with CABG or PCI; 2) compared the outcomes of CR vs. IR using any of the definitions listed in online Table 1 (14); 3) reported long-term mortality rates.

We excluded 1) studies assessing the role of PCI on the non-culprit vessel for the treatment of ST-segment elevation myocardial infarction (STEMI); 2) studies comparing outcomes of PCI for chronic total occlusion (CTO) (success vs. failure) unless the degree of completeness of revascularization was also reported, 3) studies that focused on patients with redo-CABG, and 4) single-center studies with small sample size (≤ 100 patients in each treatment arm).

Study selection Our initial search yielded 6,668 citations (Figure 1). Of these, 6,134 (92%) were excluded by title search because of irrelevant content, animal subjects, or publication in a language other than English. The abstracts of the remaining 534 studies were reviewed. Of these, 109 abstracts were deemed eligible for full text manuscript review and 425 (79.5%) were excluded for various reasons (Figure 1). Of the 109 full text manuscripts reviewed for eligibility, 24 met the inclusion criteria. Additional 11 manuscripts were identified through hand searching leading to a total of 35 studies included in this meta-analysis.

Data extraction Data were abstracted by 2 reviewers (S.G. and Y.S.) using standardized data extraction forms. Discrepancies were resolved by consensus. Abstracted information included study design, time frame, key patient and procedural characteristics, and relevant outcomes. For RCTs that reported outcomes for CABG and PCI separately we made two entries, one for each revascularization modality. When outcomes were not reported separately we included the study in the main analysis but not in the subgroup analysis of revascularization modalities.

Outcomes The primary outcome for this systematic review was all-cause mortality. Secondary outcomes were myocardial infarction (MI), and repeat revascularization.

Methodological quality

Study selection, data collection, analysis and reporting of the results were performed using the recommendations for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group (17). Heterogeneity across trials was assessed using the Cochrane Q statistic ($p < 0.1$ was considered significant) and I^2 statistic (18). I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance (18). A value of 0% indicates no heterogeneity, and larger values indicate increased heterogeneity. Publication bias was visually estimated by assessing funnel plots.

We calculated weighted risk ratios (RRs) and 95% CI for categorical variables. Each RR was calculated according to the DerSimonian-Laird random effects model. Automatic "zero cell" correction was used for studies with no events for a particular outcome. All analyses were performed using STATA software, version 10.1 (STATA Corporation, College Station, Texas).

Results

Study and patient characteristics The characteristics of the 35 studies that met eligibility criteria are displayed in Table 1 and online supplementary appendix 1. A full listing of all 35 articles is provided in online supplementary appendix 2. Of these, 28 were observational studies, 5 were subgroup analysis of RCTs, one was a subgroup analysis of a non-randomized clinical trial, and one was a single-center RCT comparing CR vs. IR. Four of the 35 studies reported outcomes for PCI and CABG separately, resulting in a total of 39 entries (Table 1). Of the 39 study entries, 34 (87%) used an anatomical definition of CR, 2 (5%) a functional definition, 2 (5%) a numerical definition, and 1 (2.5%) multiple definitions of CR. The funnel plots were not

suggestive of a publication bias (online Figures 1-3). Online supplementary appendix 3 contains the definition of MI used in each study.

The present analysis includes 89,883 patients, of which 45,417 (50.5%) received CR and 44,466 (49.5%) received IR. The revascularization modality was CABG for 25,938 patients (29%) and PCI for the remaining 63,945 patients (71%).

Mean age of the study participants was 63 (±7) years, 74% were male, 25% had diabetes mellitus, and 43% had a previous MI. The mean follow-up time was 4.6 (±4) years.

Mortality

Of the 89,883 patients included in this meta-analysis 12,259 (13%) died during follow-up. Complete revascularization was associated with reduced long-term mortality relative to IR (risk ratio [RR]: 0.71; 95% confidence interval [CI]: 0.65-0.77, p<0.001, I^2=71%) (Figure 2 and online Table 2). The mortality benefit was observed in patients treated with CABG and PCI (CABG: RR: 0.70; 95% CI: 0.61-0.80, p<0.001, I^2=80% and PCI: RR: 0.72; 95% CI: 0.64-0.81, p<0.001, I^2=62%) (Figure 3 and 4). Likewise, the mortality benefit associated with CR was seen in RCTs (RR: 0.76; 95% CI: 0.62-0.92, p=0.006, I^2=0%) and observational studies (RR: 0.70; 95% CI: 0.64-0.77, p<0.001, I^2=78%) and did not vary substantially with the definition of CR (anatomical RR: 0.73; 95% CI: 0.67-0.79, p<0.001, I^2=65% and non-anatomical RR: 0.54; 95% CI: 0.36-0.89, p=0.01, I^2=88%).

Myocardial Infarction

Eighteen out of 35 studies reported 1,509 MIs during follow-up. Compared to IR, CR was associated with lower risk of MI (RR: 0.78; 95% CI: 0.68-0.90, p=0.001, I^2=19%). A reduction in MI was observed among PCI-treated patients (PCI: RR: 0.80; 95% CI: 0.71-0.91, p=0.001, I^2=0%) but not among CABG-treated patients (CABG: RR: 0.69; 95% CI: 0.44-1.10, p=0.12, I^2=

62%). The lower risk of MI was seen in RCTs (RR: 0.72; 95% CI: 0.61-0.86, p<0.001, I^2=0%), observational studies (RR: 0.78; 95% CI: 0.61-1.00, p=0.05, I^2=44%), and studies that used an anatomical definition of CR (RR: 0.72; 95% CI: 0.63-0.83, p<0.001, I^2=0.3%). Only one study reported MI rates using a non-anatomical definition of CR (RR: 0.99; 95% CI: 0.74-1.25, p=0.79).

Repeat Coronary Revascularization

Twenty out of 35 studies reported 5,756 repeat revascularization procedures during follow-up. Compared to IR, CR was associated with lower risk of repeat revascularization procedures (RR: 0.74; 95% CI: 0.65-0.83, p<0.001, I^2=65%). Complete revascularization was associated with less repeat revascularization procedures among PCI- (RR: 0.72; 95% CI: 0.63-0.81, p<0.001, I^2=70%) but not CABG-treated patients (RR: 0.92; 95% CI: 0.67-1.28, p=0.64, I^2=22%). The benefit of CR in reducing repeat revascularization procedures was seen in RCTs (RR: 0.67; 95% CI: 0.60-0.75, p<0.001, I^2=0%) and observational studies (RR: 0.79; 95% CI: 0.66-0.95, p=0.01, I^2=76%). Complete revascularization was associated with a reduced need for repeat coronary revascularization in studies that used an anatomical definition of CR (RR: 0.74; 95% CI: 0.66-0.83, p<0.001, I^2=54%). Only one study reported repeat revascularization rates using a non-anatomical definition of CR (RR: 0.55; 95% CI: 0.44-0.67, p<0.001).

Discussion

The results of this systematic review and meta-analysis of CR vs. IR in patients with multivessel CAD show that CR is more often achieved with CABG than PCI and is associated with a 30% reduction in long-term mortality, a 22% reduction in MI, and a 26% reduction in repeat coronary revascularization procedures. The lower mortality associated with CR was seen in both PCI- and

CABG-treated patients, and was independent of the study design and definition of complete revascularization.

The association between CR and lower risk for subsequent cardiovascular events may be causal. CR may improve clinical outcomes by reducing or eliminating myocardial ischemia, which has been linked to worse prognosis, especially when large (19). CR may improve exercise capacity, reduce the risk of arrhythmic events and improve tolerance to future acute coronary ischemic events (20). Alternatively, IR may be a surrogate marker for higher baseline ischemic burden and more advanced coronary artery disease that is less amenable to revascularization by either PCI or CABG.

The findings of this study have several practical implications for cardiologists and surgeons alike. First, given the strong clinical benefit in patients with multivessel disease CR may be the optimal revascularization strategy. The likelihood of achieving CR with either revascularization modality, ideally estimated by a heart team approach, should influence the decision to proceed with CABG or PCI. With this approach in the SYNTAX (SYNergy between PCI with TAXus and Cardiac Surgery) trial (21) the rates of incomplete revascularization were 43.3% for PCI and 36.8% for CABG, which compares favorably with historical cohorts (13), while still highlighting the procedural complexity of achieving CR. The most common reasons for not achieving CR with PCI in SYNTAX were the presence of chronic total occlusions (CTO) (OR: 2.46, 95% CI: 1.81-3.39, $p<0.01$), bifurcation disease (OR: 1.44, 95% CI: 1.09-1.89, $p=0.01$), and diffuse disease or small vessels (< 2 mm) (OR: 1.53, 95%CI: 1.12-2.10, $p<0.008$) (22). Overall, the SYNTAX score, a surrogate marker for disease complexity, was higher in IR than in CR patients (31.4 ± 11 vs. 26.2 ± 10, $p < 0.01$) (22). Many of the barriers for achieving CR with PCI are no longer considered insurmountable (23). For example, CTO-PCI has evolved dramatically over

the last decade with experienced operators reporting recanalization rates of 80%-90% with advanced CTO techniques such as dual injections, antegrade dissection re-entry, and retrograde wiring (24-26). The most common reasons for not achieving CR with CABG were unstable angina presentation (OR: 1.37, 95% CI: 1.01-1.85, p =0.04), diffuse disease or small vessels (OR: 2.10, 95% CI: 1.51-2.93, p<0.001), and number of lesions (OR: 1.71, 95% CI: 1.55-1.90, p<0.001) (20). Some of those barriers may be hard to overcome; bypassing small vessels is associated with higher rates of saphenous vein graft failure and some patients may not have enough saphenous vein conduits to allow revascularization of all potential coronary targets. Based on data from the BARI (Bypass Angioplasty Revascularization Investigation) trial and others (27) showing no survival disadvantage when non-LAD (left anterior descending artery) territories were left ungrafted many surgeons have advocated the concept of incomplete "reasonable" revascularization mainly as an attempt to limit aortic cross-clamp time (28-31). Our study cannot address this issue, yet it would suggest that leaving potentially viable and graftable target coronary arteries unresvacularized is not prudent.

Second, the mortality benefit seen in this meta-analysis with CR was of about the same magnitude (~30%) in patients receiving CABG or PCI, which suggests that the revascularization modality may not be as important as the objective of achieving complete revascularization. For example, in the SYNTAX trial for patients in the lowest tercile of the SYNTAX score (≤22) IR rates between PCI and CABG were not dissimilar (31% vs. 27%) and no statistical difference in major adverse cardiac or cerebrovascular events (MACCE) was seen between PCI (13.6 %) and CABG (14.7%) at 1-year (p=0. 71) (21). In contrast, for patients in the highest tertile of the SYNTAX score (≥33) as the rates of incomplete revascularization increased disproportionately for PCI patients (57%) so did MACCE rates, which were 23.4% for PCI and 10.9%for CABG

($p<0.001$) at 1-year and 34% and 19% at 3-years ($p<0.001$), respectively (30). Our study extends this observation by demonstrating that CR may provide similar relative reduction in the risk of major adverse cardiovascular events in patients treated with either PCI or CABG.

Third, although the majority of studies (87%) included in this meta-analysis used an anatomical definition of CR, the results did not change significantly for the hard end-point of long-term mortality when a non-anatomical definition of CR was used. For the outcomes of MI and repeat revascularization only one study reported event rates using a non-anatomical definition.

One of the limitations of current data is lack of a standardized, universal definition of what constitutes an incomplete revascularization procedure (14,29). Gössl et al. recently proposed a universal definition of IR using coronary angiography and fractional-flow reserve (FFR) data (31). The proposed definition of incomplete anatomical and functional revascularization is based on the inability to treat 1) all coronary segments that have a ≥50% to 70% diameter stenosis and an FFR ≤0.80 or 2) > 70% stenosis without FFR that supply a significant degree of viable myocardium. Based on the previous work by Piljs et al. regarding the excellent long-term outcomes of patients with intermediate stenosis and insignificant FFR (32) and the observation that FFR-guided PCI in patients with multivessel CAD is superior to angiography-guided PCI (33) a definition of IR that includes anatomy and physiology seems intuitive, although it requires prospective validation.

Finally, the finding that in patients treated with CABG CR was not associated with a reduction in MI or repeat revascularization procedures may be due to the small number of studies that reported those outcomes. Alternatively, the degree of completeness of revascularization may not be as important in reducing MI or repeat procedures in CABG as long as the 3 major epicardial vessels are grafted (27).

Limitations Our study has important limitations. First, observational studies and post-hoc analysis of randomized clinical trials were included in this meta-analysis. Many of these studies had different entry criteria, study populations, and follow-up time. This is a source of increased heterogeneity that may limit the generalisability of our conclusions to the broader multivessel coronary artery disease population (18). However, the beneficial effects of CR in terms of reducing mortality, MI and repeat revascularization procedures persisted when the analysis was restricted to RCTs with similar entry criteria and low heterogeneity ($I^2 < 25\%$). Second, it is plausible that IR could be a surrogate marker for residual CAD or other important comorbidities that, while not amenable to revascularization, would place patients at risk of adverse clinical events (CTO, small vessel disease, etc). It should be emphasized that only one RCT included in this meta-analysis randomized patients to IR vs. CR. The remainder are direct comparisons of CABG vs. PCI in which the decision to perform IR or CR was not randomized, and therefore was subject to potential bias. Only an RCT directly comparing CR vs. IR can answer this question. The finding that CR was superior to IR even in RCTs that required equivalent complete anatomical revascularization prior to patient enrollment suggests that selection bias alone is unlikely to explain our findings. Third, caution is advised when extrapolating our findings to patients with multivessel CAD undergoing primary PCI for STEMI as these patients were not included in our study. Fourth, the extent of IR could not be quantified. It is possible that IR of a small myocardial territory would carry less risk than IR of a large or multiple myocardial segments. Fifth, for PCI-treated patients, the outcome of repeat coronary revascularization should be interpreted with caution, as it is likely that in some of the studies included in this meta-analysis staged PCIs were counted as a repeat revascularization procedure. Therefore, repeat coronary revascularization may simply represent part of an initial procedural strategy rather than

inadequate response to medical therapy or restenosis. Finally, the role of contemporary medical therapy in patients with residual CAD, although not the focus of our study, should not be underestimated (32). Optimization and standardization of medical therapies based on residual CAD burden has the potential to improve clinical outcomes.

Conclusions

In this first systematic review and meta-analysis of CR vs. IR in patients with multivessel CAD undergoing revascularization with CABG or PCI, CR was associated with lower morbidity and mortality. Hence the likelihood of achieving CR with either revascularization modality should inform the decision to proceed with CABG or PCI.

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Figure Legends:

Figure 1: **Flow diagram of the literature search and study selection.**

A total of 6,668 citations were identified through database searching and 109 full text manuscripts were reviewed for eligibility, of which 24 met the inclusion criteria. Eleven manuscripts were identified through hand searching leading to a total of 35 studies included in this meta-analysis.

Figure 2: Pooled analysis with risk ratios (RR) and 95% confidence intervals (95% CI) for the occurrence of total mortality.

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. CR= complete revascularization, IR= incomplete revascularization.

Figure 3: Pooled analysis in CABG studies.

Pooled analysis with risk ratios (RR) and 95% confidence intervals for the occurrence of total mortality in CABG studies. 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. CR= complete revascularization, IR= incomplete revascularization.

Figure 4: Pooled analysis in PCI studies.

Pooled analysis with risk ratios (RR) and 95% confidence intervals for the occurrence of total mortality in PCI studies. 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. CR= complete revascularization, IR= incomplete revascularization.

Online-Only Material:

Figure Legend for Online Figures 1, 2, and 3: Funnel Plots and 95% pseudo confidence limits for visual assessment of publication bias. 1- Mortality, 2- Myocardial Infarction, 3- Repeat Revascularization

Online-Only Supplementary Appendix 1:

References to Table 1

1- The authors used 4 different definitions of complete revascularization. For the purpose of this meta-analysis we used definition #1 (CR-1): angioplasty or grafting of all diseased coronary segments ≥ 1.5 mm.

2- These studies focused on elderly patients.

3- This study focused on patients undergoing off-pump coronary artery bypass surgery

4- In this trial interventional cardiologists were required to plan for complete or incomplete revascularization prior to the procedure. According to this pre-procedural assessment 2 groups were created: planned complete revascularization (CR) or planned incomplete revascularization (IR). The initial strategy was further characterized after the procedure as all lesions successfully treated (all successful) or not all lesions successfully treated (not all successful). For the purpose of this meta-analysis CR was comprised of patients with a pre-procedural strategy of CR that was all successful whereas the IR group was comprised of patients in whom pre-procedural IR was planned and successful.

5- Outcomes were reported for various high-risk subsets of IR patients: 1- chronic total occlusion (CTO) and at least one other vessel incompletely revascularized (n=1,321), 2- single total occlusion (n=3,232), 3- two or more vessels incompletely revascularized with no CTO (n=2,057), and 4- one incompletely revascularized vessel with no CTO (n=8,518). For the purpose of this meta-analysis mortality is reported for the entire cohort of IR patients (n=15,128). For the outcome of repeat revascularization, the group comprised of two or more IR vessels without a CTO was used as the IR group.

6- This study was a comparison of CTO-PCI success vs. failure with drug-eluting stents. Cardiac mortality for complete and incomplete revascularization groups was reported and therefore this manuscript was included in the meta-analysis.

7- This study used a quantitative angiographic definition of incomplete revascularization based on various diameter stenosis (DS) cutoffs (≥30%, ≥40%, ≥50%, ≥60%, ≥ 70%) that remained after PCI in vessels ≥ 2 mm. For the purpose of this meta-analysis we used ≥ 50% cutoff to define IR.

8- This study focused in patients with diabetes mellitus.

9- This study makes a distinction between two forms of incomplete revascularization (IR): 1- by operator choice, 2- technically unachievable. For the purpose of this meta-analysis we selected IR by operator choice as our IR group.

10- This study characterized patients with incomplete revascularization (IR) as belonging to one of three groups according to the number of remaining lesions after PTCA with ≥50% residual stenosis (1, 2 or ≥3). For the purpose of this meta-analysis we selected patients with ≥3 residual lesions after PTCA as our IR group.

11- Results are presented for 3803 pairs of propensity-matched patients, which represent 58% of the total cohort comprised of 13,016.

* Prevalence of diabetes in the IR group.

† A range is presented when studies reported separate counts for complete and incomplete revascularization. Mean and/or median values for the entire cohort are presented whenever available. For all calculations of mean and/or median values for which we did not have a measure for the entire cohort the numbers reflect mean and/or median values for the IR group.

Online-Only Supplementary Appendix 2: A list of the 35 studies included in the meta-analysis is provided in alphabetical order

1. Appleby CE, Mackie K, Dzavík V, Ivanov J. Late outcomes following percutaneous coronary interventions: results from a large, observational registry. Can J Cardiol. 2010 Aug-Sep;26(7):e218-24.

2. Bourassa MG, Kip KE, Jacobs AK, Jones RH, Sopko G, Rosen AD, Sharaf BL, Schwartz L, Chaitman BR, Alderman EL, Holmes DR, Roubin GS, Detre KM, Frye RL. Is a strategy of intended incomplete percutaneous transluminal coronary angioplasty revascularization acceptable in nondiabetic patients who are candidates for coronary artery bypass graft surgery? The Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol. 1999 May;33(6):1627-36.

3. Breeman A, Boersma E, Van Den Brand MJ, Van Herwerden L, Serruys PW. Completeness of revascularization by percutaneous coronary intervention. Neth Heart J 2001;9:3-9.

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5. Deligonul U, Vandormael MG, Kern MJ, Zelman R, Galan K, Chaitman BR. Coronary angioplasty: a therapeutic option for symptomatic patients with two and three vessel coronary disease. J Am Coll Cardiol. 1988 Jun;11(6):1173-9.

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10. Jones EL, Craver JM, King SB, 3rd, et al. Clinical, anatomic and functional descriptors influencing morbidity, survival and adequacy of revascularization following coronary bypass. Ann Surg. Sep 1980;192(3):390-402.

11. Jones EL, Weintraub WS. The importance of completeness of revascularization during long-term follow-up after coronary artery operations. J Thorac Cardiovasc Surg. 1996 Aug;112(2):227-37.

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13. Kip KE, Bourassa MG, Jacobs AK, Schwartz L, Feit F, Alderman EL, Weiner BH, WeissMB, Kellett MA Jr, Sharaf BL, Dimas AP, Jones RH, Sopko G, Detre KM. Influence of pre-PTCA strategy and initial PTCA result in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 1999 Aug 31;100(9):910-7.

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15. 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. Jul 2001;79(2-3):197-205.

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32. Vander Salm TJ, Kip KE, Jones RH, et al. What constitutes optimal surgical revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol. Feb 20 2002;39(4):565-572.

33. Vieira RD, Hueb W, Gersh BJ, et al. Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. Circulation. Sep 11 2012;126(11 Suppl 1):S158-163.

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Online-Only Supplementary Appendix 3: Definition of Myocardial Infarction

1. **Van der Brand et al.** The effects of Completeness of Revascularization on Event-Free Survival at One Year in the ARTS trial. Definition obtained from original publication: Serruys PW et al. N Engl J Med 2001; 344:117-24.

   In the first seven days after the intervention, a definite diagnosis of myocardial infarction was made if there was documentation of new abnormal Q waves (according to the Minnesota code) and either a ratio of serum creatine kinase MB (CK-MB) isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value that was five times the upper limit of normal. Serum creatine kinase and CK-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Beginning eight days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of myocardial infarction. This two-part method of defining myocardial infarction was used to eliminate the difficulty of diagnosing a myocardial infarction after surgery. A myocardial infarction wasconfirmed only after the relevant electrocardiograms had been analyzed by the electrocardiographic core laboratory and adjudicatedby a clinical-events committee. All revascularization procedures after the initial intervention and the reasons for them were recorded.

2. **Sarno et al.** Impact of Completeness of Revascularization on the Five-Year Outcome in Percutaneous Coronary Intervention and Coronary Artery Bypass Graft Patients (from the ARTS-II Study).

Myocardial infarction was defined in the first 7 days after the intervention, if there was documentation of new abnormal Q waves and a ratio of serum creatinine kinase-MB isoenzyme to total creatinine that >0.1 or a creatine kinase-MB value that was 5 times the upper-limit of normal. Serum creatinine kinase and creatine kinase-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Commencing 8 days after the intervention (length of hospital stay after surgery), abnormal Q waves or enzymatic changes, as described earlier, were sufficient for a diagnosis of myocardial infarction. Myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the core laboratory and adjudicated by the clinical events committee. Incidence of stent thrombosis was determined according to Academic Research Consortium definitions.

3. **Kim Y et al.** Impact of Angiographic Complete Revascularization After Drug-Eluting Stent Implantation or Coronary Artery Bypass Graft Surgery for Multivessel Coronary Artery Disease.

A diagnosis of MI was defined as either complications at index admissions (defined as new pathological Q waves after index treatment) or follow-up MI requiring subsequent hospitalization (defined as an emergency admission with a principal diagnosis of MI), as described. Q-wave MI was defined as the documentation of a new pathological Q wave after index treatment.

4. **Head JS et al.** Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data.

   MI was defined in relation to intervention status as follows: (i) after allocation but before treatment: Q-wave [new pathological Q-waves in >2 leads lasting >0.04 s with creatine kinase-MB (CK-MB) levels above normal] and non-Q-wave MI [elevation of CK levels >2x the upper limit of normal (ULN) with positive CK-MB or elevation of CK levels to >2x ULN without new Q-waves if no baseline CK-MB was available]; (ii) <7 days after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5x ULN; and (iii) >7 days after intervention: new Q-waves or peak CK-MB/total CK>10% or plasma level of CK-MB 5x ULN or plasma level of CK 5x ULN. The CK/CK-MB enzyme levels were obtained and measured by a core laboratory for all randomized patients. All events were adjudicated by a Clinical Event Committee.

5. **Vieira RD et al.** Effect of Complete Revascularization on 10-Year Survival of Patients with Stable Multivessel Coronary Artery Disease MASS II Trial.

   ** Definition obtained from original publication: Hueb W et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic

strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardio 2004;43:1743-1751.

Myocardial infarction was defined as the presence of significant new Q waves in at least two electrocardiographic (ECG) leads or symptoms compatible with MI associated with creatine kinase, MB fraction concentrations that were more that three times the upper limit of the reference range.

6. **Jones EL et al.** Clinical, Anatomic and Functional Descriptors Influencing Morbidity, Survival and Adequacy of Revascularization Following Coronary Bypass.

Unstable angina was defined according to the criteria of Logue, King and Hurst and did not require the presence of electrocardiographic changes. Perioperative infarction was said to have occurred if there was development of electrocardiographic new Q waves at least 0.04 seconds duration.

7. **Scott R et al.** Isolated bypass grafting of the left internal thoracic artery to the left anterior descending coronary artery: late consequences of incomplete revascularization.

Myocardial infarction was not an endpoint (NR: not reported).

8. **Vander Salm TJ et al**. What Constitutes Optimal Surgical Revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI).

Definition obtained from protocol publication: The BARI Protocol. Protocol for the Bypass Angioplasty Revascularization Investigation. Circulation 1991;84 [suppl V]:V-1-V-27).

MI-when MI is suspected, all ECGs that are recorded within 3 days after the event are sent to the Central ECG Laboratory, and a Suspected MI report form is required. These data are used to determine whether the event was an MI. When data are missing or inconsistent, the MMCC reviews all available data to determine whether an MI occurred. MIs that do not result in hospitalization will be identified through the yearly scheduled ECGs.

9. **Kleisli T et al. In** the current era, complete revascularization improves survival after coronary artery bypass surgery.

   Myocardial infarction was not an endpoint (NR: not reported).

10. **Rastan JA et al.** Does Reasonable Incomplete Surgical Revascularization Affect Early or Long-Term Survival in Patients With Multivessel Coronary Artery Disease Receiving Left Internal Mammary Artery Bypass to Left Anterior Descending Artery?

    Onset of postoperative acute myocardial infarction was defined as type 5 (associated with CABG), according to the Consensus Document for universal definition of myocardial infarction.

11. **Kosower BD et al.** Impact of Complete Revascularization on Long-Term Survival After Coronary Artery Bypass Grafting in Octogenarians.

Myocardial infarction was not an endpoint (NR: not reported).

12. **Caputo M et al.** Incomplete Revascularization During OPCAB Surgery is Associated With Reduced Mid-Term Event-Free Survival.

Non-fatal cardiac-related events included: (1) the need for a further coronary revascularization procedure (whether reoperation or percutaneous transluminal coronary angioplasty); (2) patient reported hospital attendance for myocardial infarction, coronary angiography, congestive heart failure, or recurrent angina.

13. **Osswald BR et al.** Does the completeness of revascularization affect early survival after coronary artery bypass grafting in elderly patients?

Myocardial infarction was not an endpoint (NR: not reported).

14. **Mohammadi S et al.** Completeness of Revascularization and Survival Among Octogenarians With Triple-Vessel Disease.

MI was defined as the appearance of a new Q wave on electrocardiography in conjunction with an elevation of the plasma creatine kinase-MB fraction greater than or equal to 5 times the upper limit of normal.

15. **Jones EL et al.** The importance of completeness of revascularization during long-term follow-up after coronary artery operations.

No definition is provided in the manuscript.

16. **McNeer JF et al.** Complete and incomplete revascularization at aortocoronary bypass surgery: Experience with 392 consecutive patients.

Myocardial infarction was not an endpoint (NR: not reported).

17. **Tyras DH et al.** Long-Term Resuts of Myocardial Revascularization.

The occurrence of perioperative myocardial infarction was identified by analysis of serial postoperative electrocardiograms and cardiac isoenzymes as previously described. At least three serial postoperative electrocardiograms were performed in all patients. Total serum creatine kinase, lactic dehydrogenase and glutamic oxaloacetic transaminase levels were measured in all patients on the 1^{st} and 2^{nd} postoperative days. Determinations of isoenzymes of lactic dehydrogenase and creatine kinase were performed in 83 percent of patients. In patients with a normal electrocardiogram without isoenzyme analysis perioperative

myocardial infarction was considered to have occurred if glutamic oxaloacetic transaminase levels were greater than 100 mU/ml and total creatine kinase exceeded 400 S.U. or total lactic dehydrogenase exceeded 400 mU/ml.

18. **Kip K et al.** Influence of Pre-PTCA Strategy and Initial PTCA Result in Patients With Multivessel Disease. The Bypass Angioplasty Revascularization Investigation (BARI).

Resting ECGs were collected at study entry, before and after all coronary revascularization procedures, at scheduled follow-up, and for suspected myocardial infarction (MI) events. A central ECG laboratory coded all Q-wave events. According to protocol, cardiac enzymes were not used to define MI within 96 hours of revascularization.

Definition obtained from protocol publication: The BARI Protocol. Protocol for the Bypass Angioplasty Revascularization Investigation. Circulation 1991;84 [suppl V]:V-1-V-27).

MI-when MI is suspected, all ECGs that are recorded within 3 days after the event are sent to the Central ECG Laboratory (in-depth information about the Central Electrocardiographic Laboratory [CEL] may be found in Appendix 7), and a Suspected MI report form is required. These data are used to determine whether the event was an MI. When data are missing or inconsistent, the MMCC reviews all available data to determine whether an MI occurred. MIs that do not result in hospitalization will be identified through the yearly scheduled ECGs.

19. **Bourassa MG et al.** Is a Strategy of Intended Incomplete Percutaneous Transluminal Coronary Angioplasty Revascularization Acceptable in Nondiabetic Patients Who Are Candidates for Coronary Artery Bypass Graft Surgery?

Rest electrocardiograms were routinely collected at study entry, before and after all coronary revascularization procedures, at scheduled follow-up and for all suspected myocardial infarct events. A central electrocardiographic laboratory coded all Q-wave events blinded by initial treatment assignment. According to protocol, cardiac enzymes were not used to define myocardial infarction within 96 hours of a revascularization procedure. Cause of death was classified by an independent Mortality and Morbidity Classification Committee. Cardiac death was defined as: death less than 1 h after onset of cardiac symptoms, or within 1 h to 30 days after a documented or probable myocardial infarction, or death from intractable congestive heart failure, cardiogenic shock or other documented cardiac causes.

Definition obtained from protocol publication: The BARI Protocol. Protocol for the Bypass Angioplasty Revascularization Investigation. Circulation 1991;84 [suppl V]:V-1-V-27).

Myocardial Infarction: When MI is suspected, all ECGs that are recorded within 3 days after the event are sent to the Central ECG Laboratory and a Suspected MI report form is required. These data are used to determine whether the event was an MI. When data are missing or inconsistent, the MMCC reviews all available data to determine whether an MI occurred. MIs that do not result in hospitalization will be identified through the yearly scheduled ECGs.

20. **Ijsselmuiden A et al.** Complete versus culprit vessel percutaneous coronary intervention in multivessel disease: A randomized comparison.

The diagnosis of MI was based on prolonged chest pain associated with either new >0.03-second Q waves on the surface electrocardiogram or a rise in creatine kinase enzyme >200 U/L or in its MB fraction >20 U/L. Serial enzymes were measured or electrocardiograms recorded only in the event of signs or symptoms consistent with myocardial ischemia.

21. **Valenti R et al.** Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion.

Non-W-wave MI was defined as an increase in creatine kinase-MB fraction of three times the upper limit of normal, or for patients with elevated values on admission as a re-elevation of creatine kinase-MB values. Creatine kinase-MB fraction was routinely assessed 12h after PCI in all patients or at least three times every 6 h in patients with recurrent chest pain. A Q-wave MI was defined as new Q-wave in two or more contiguous leads in addition creatine kinase-MB elevation.

22. **Hanna EL et al.** Impact of Completeness of Percutaneous Coronary Intervention Revascularization on Long-Term Outcomes in the Stent Era.

Myocardial infarction was not an endpoint (NR: not reported).

23. **Wu C et al.** Impact of Incomplete Revascularization on Long-term Mortality After Coronary Stenting.

Myocardial infarction was not an endpoint (NR: not reported).

24. **Hannan et al.** Incomplete Revascularization in the Era of Drug-Eluting Stents.

Myocardial infarctions occurring after PCI during the index admission were defined in PCIRS as new Q waves and a rise in cardiac enzyme to at least 2.5 times the normal range. Myocardial infarctions occurring after discharge were obtained using Statewide Planning and Research Cooperative System data and were defined as readmissions with International Classification of Diseases-Ninth Revision-Clinical Modification code 410.x1 as a principal diagnosis.

25. **Rosner GF et al.** Impact of the Presence and Extent of Incomplete Angiographic Revascularization After Percutaneous Coronary Intervention in Acute Coronary Syndromes. The Acute Catherization and Urgent Intervention Triage Strategy (ACUITY) Trial.

** Definition referred in Stone GW et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-16; which then refers to paper by Stone GW et al:

Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial: Study Design and Rationale. Am Heart J 2004;148:764-75.

Myocardial infarction: (A) MI diagnosis before angiography, or, in medically treated patients. Patients with unstable angina (without NSTEMI): Any elevation of troponin or CPK-MB (or CPK) greater than the upper limits of normal (ULN).(B) MI diagnosis before angiography, or, in medically treated patients. Patients with NSTEMI: (1) If the peak troponin or CPK-MB (or CPK) has not yet been reached: Recurrent chest pain lasting >30 minutes, or new electrocardiographic changes consistent with MI and the next troponin or CPK-MB (or CPK) level measured approximately 8 to 12 hours after the event be elevated by at least 50% above the previous level. (2) If the elevated troponin or CPK-MB (or CPK) levels are falling or have returned to normal: A new elevation of troponin or CPK-MB (or CPK) > ULN if the troponin or CPK-MB (or CPK) level has returned to ULN, or arise by >50% above the previous nadir level if the troponin or CPK-MB (or CPK) level has not returned to ULN.

(C) MI diagnosis after PCI. Patients with or without NSTEMI: If the elevated CPK-MB (or CPK) levels are falling or are normal: any CPK-MB (or CPK) ≥3 X ULN within 24 hours after PCI that is also increased at least 50% over the most recent pre-PCI levels, or new, significant Q waves in ≥2 contiguous electrocardiographic leads with CPK-MB (or CPK) >ULN. (D) MI after PCI.

Patients with NSTEMI: If the peak CPK-MB (or CPK) has not yet been reached before PCI: Recurrent chest pain ≥30 minutes, or new electrocardiographic changes consistent with a second MI and the next CPK-MB (or CPK) level measured approximately 8 to 12 hours after

the event is elevated by at least 50% above the previous level; or new, significant Q waves in ≥2 contiguous electrocardiographic leads. (E) MI diagnosis after CABG. Any CPK-MB (or CPK) >10 x ULN within 24 hours of CABG and increased at least 50% over the most recent pre-CABG levels, or any CPK-MB (or CPK) ≥ 5 x ULN within 24 hours of CABG and increased at east 50% over the most recent pre-CABG levels and new, significant Q waves in ≥2 contiguous electrocardiographic leads.(F) Q-wave versus non–Q-wave MI. Once the enzymatic criteria for MI are met, a Q-wave MI will be diagnosed if new pathologic Q-waves develop in ≥2 electrocardiographic contiguous leads as adjudicated by the Clinical Events Committee. An MI not meeting this definition will be considered a non–Q-wave MI.

26. **Nikolsky E et al.** Percutaneous Coronary Interventions in Diabetic Patients: Is Complete Revascularization Important?

Q-wave MI was diagnosed when there was elevation in creatinine kinase to twice the normal level with new pathological Q-waves on the electrocardiogram. MACEs were defined as cardiac death, Q-wave MI, CABG or repeat PCI.

27. **Tamburino C et al.** Complete versus Incomplete Revascularization in Patients With Multivessel Disease Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents.

MI was defined as the occurrence of ischemic symptoms in the presence of EKG changes and rise of biochemical markers of myocardial necrosis.

28. **Mariani G et al**. Complete or Incomplete Percutaneous Coronary Revascularization in Patients With Unstable Angina in Stent Era: Are Early and One-Year Results Different?

A Q-wave myocardial infarction was defined as new pathological Q-waves on the ECG in conjunction with elevation in creatine-kinase greater than twice the upper limit of normal. A non-Q-wave myocardial infarction was defined by an elevation of the cardiac enzymes greater than twice the upper limit of normal without the development of new pathological Q-waves.

29. **Srinivas V et al.** Completeness of Revascularization for Multivessel Coronary Artery Disease and Its Effect on One-Year Outcome: A Report from the NHLBI Dynamic Registry.

Myocardial infarction (MI) was defined as evidence of two or more of the following: (1) clinical symptoms; (2) ECG evidence of myocardial ischemia; (3) elevation of creatine kinase-MB >5% of total creatine kinase, total creatine kinase >2x normal, lactic dehydrogenase-II, or troponin >0.2 ng/ml; and (4) new wall motion abnormalities.

30. **Kloeter U et al.** Long-term outcome of angioplasty for multivessel coronary disease: importance and price of complete revascularization.

No definition is provided in the manuscript.

31. **Breeman A et al.** Completeness of revascularization by percutaneous coronary intervention.

No definition is provided in the manuscript.

32. **Norwa-Otto B et al.** Functionally driven complete vs incomplete revascularization in multivessel coronary artery disease – long-term results from a large cohort.

The diagnosis of Q-wave MI had to be confirmed by echocardiography showing akinesis or dyskynesis of the left ventricular (LV) wall corresponding with ECG changes.

33. **Appleby CE et al.** Late outcomes following percutaneous coronary interventions: Results from a large, observational registry.

The definition of periprocedural MI was more inclusive than that of the ACC/AHA criteria, including all patients with creatine kinase elevations two or more times the upper limit of normal.

Late MI was defined by ICD codes (see below).
Long-term follow up data were obtained through linkage of the clinical database to the Discharge Abstract Database of the Canadian Institute for Health Information and the

Registered Persons Database using encrypted health card numbers. All time-to-event analyses were conducted at the ICES in Ontario. Date were available on time-to-even for all-cause mortality, repeat PCI or subsequent CABG surgery as well as **hospitalization for MI**, heart failure or stroke (defined by the International Statistical Classification of Disease and Related Health Problems, 10th Revision coding for admission).

34. **Deligonul et al.** Coronary Angioplasty: A Therapeutic Option for Symptomatic Patients With Two and Three Vessel Coronary Disease.

    No definition is provided in the manuscript.

35. **Yang HH et al.** The Influence of Complete Coronary Revascularization on Long-term Outcomes in Patients with Multivessel Coronary Heart Disease Undergoing Successful Percutaneous Coronary Intervention.

    No definition is provided in the manuscript.

Online Table 1. Definitions of Complete Revascularization (CR) Used in Observational Studies and Clinical Trials.

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 graft (or 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 ≤ 0.75 -0.80 receive a graft or stent

PCI= percutaneous coronary intervention, CR= complete revascularization

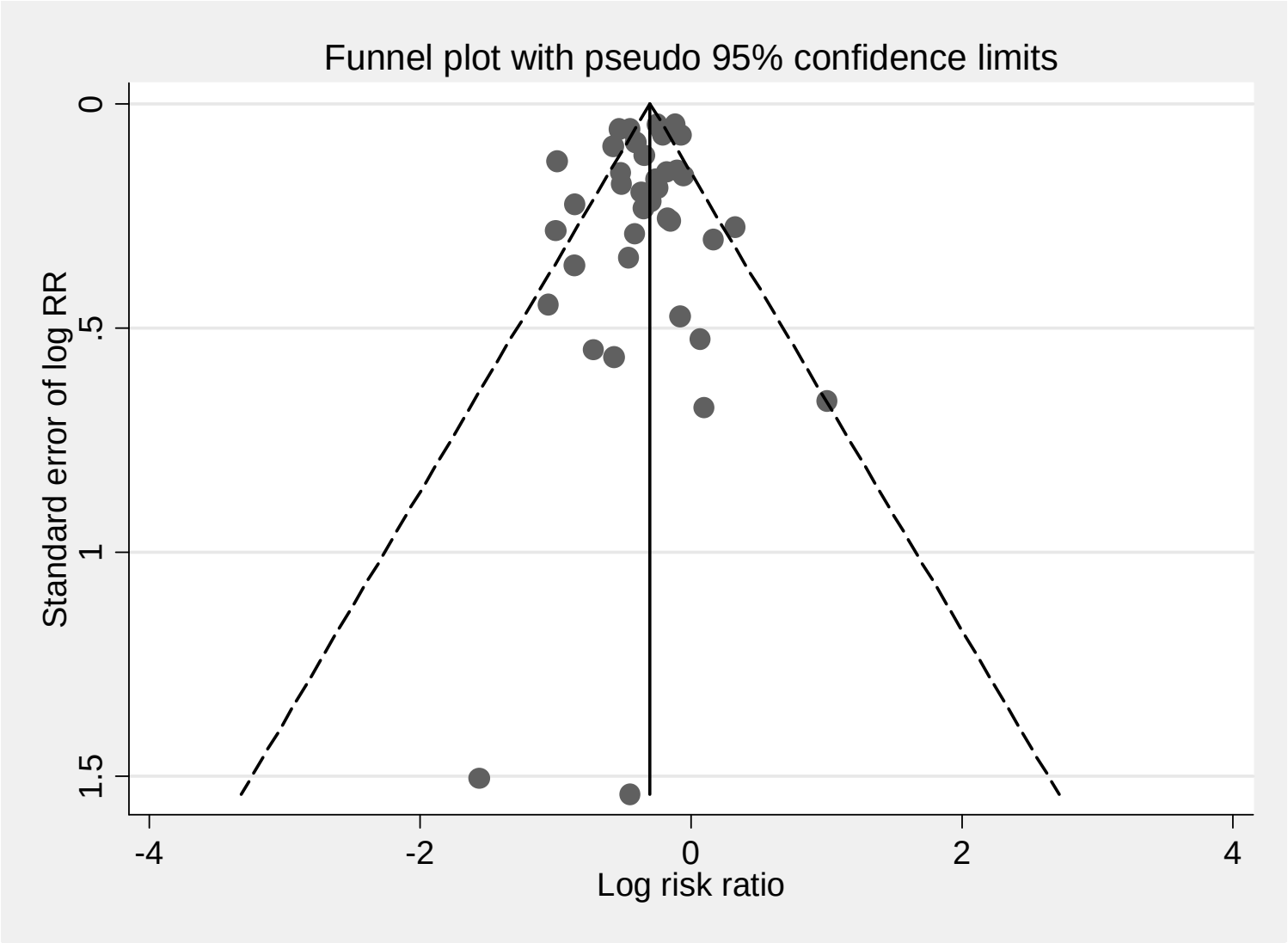
Online Table 2: Total number of patients and events in each group for the primary end-point of the study.

Study Name /First Author	CR Total	CR Events death	IR Total
ARTS I CABG/van der Brand	477	12	90
ARTS I PCI/ van der Brand	406	7	170
ARTS II PCI/ Sarno	360	16	228
Asian Medical Center/Kim CABG cohort	344	45	170
Asian Medial Center/ Kim PCI cohort	573	35	827
SYNTAX CABG/Head	550	34	320
SYNTAX PCI/ Head	508	38	388
MASS II CABG/ D'Oliveira Vieira	143	35	55
MASS II PCI/ D'Oliveira Vieira	81	14	111
Emory/Jones	2857	257	952
Cleveland /Scott	1276	383	791
BARI/ Van der Salm	1253	182	254
Cedars Sinai/Kleisli	937	165	97
Leipzig/Rastan	7870	1400	936
Wash U/Kozower	400	244	100
Bristol Heart Institute/Caputo	1242	58	237
University of Heidelberg/ Osswald	726	105	133
Quebec Heart and Lung University Institute/ Mohammad	391	141	85
BARI trial and registry/ Kip	595	55	399
BARI/ Bourassa	579	72	317
Erasmus University/ Ijsselmuiden	108	8	111
New York State registry/ Hannan	6817	586	15128
New York State registry/ Hannan	3499	165	7795
Careggi Hospital/ Valenti	301	18	185
ACUITY/ Rosner	1851	39	1103
Nikolsky	94	8	258
University of Catania/ Tamburino	212	6	296
Legnano Italy/ Mariani	49	0	159
NHLBI dynamic registry/ Srinivas	315	14	1091
Basel University Hospital/ Kloeter	101	0	149
CABRI / Breeman	148	8	119
Emory/Jones	2057	605	803
New York State/Wu	3803	731	3803
Henan Province/Yang	99	3	255
Duke/McNeer	186	69	206
Warsaw Institute of Cardiology/ Norwa-Otto	284	46	624
University of Toronto/ Appleby	2699	351	5025
Saint Louis University/ Tyras	1108	93	441
Saint Louis University/ Deligonul	118	6	255

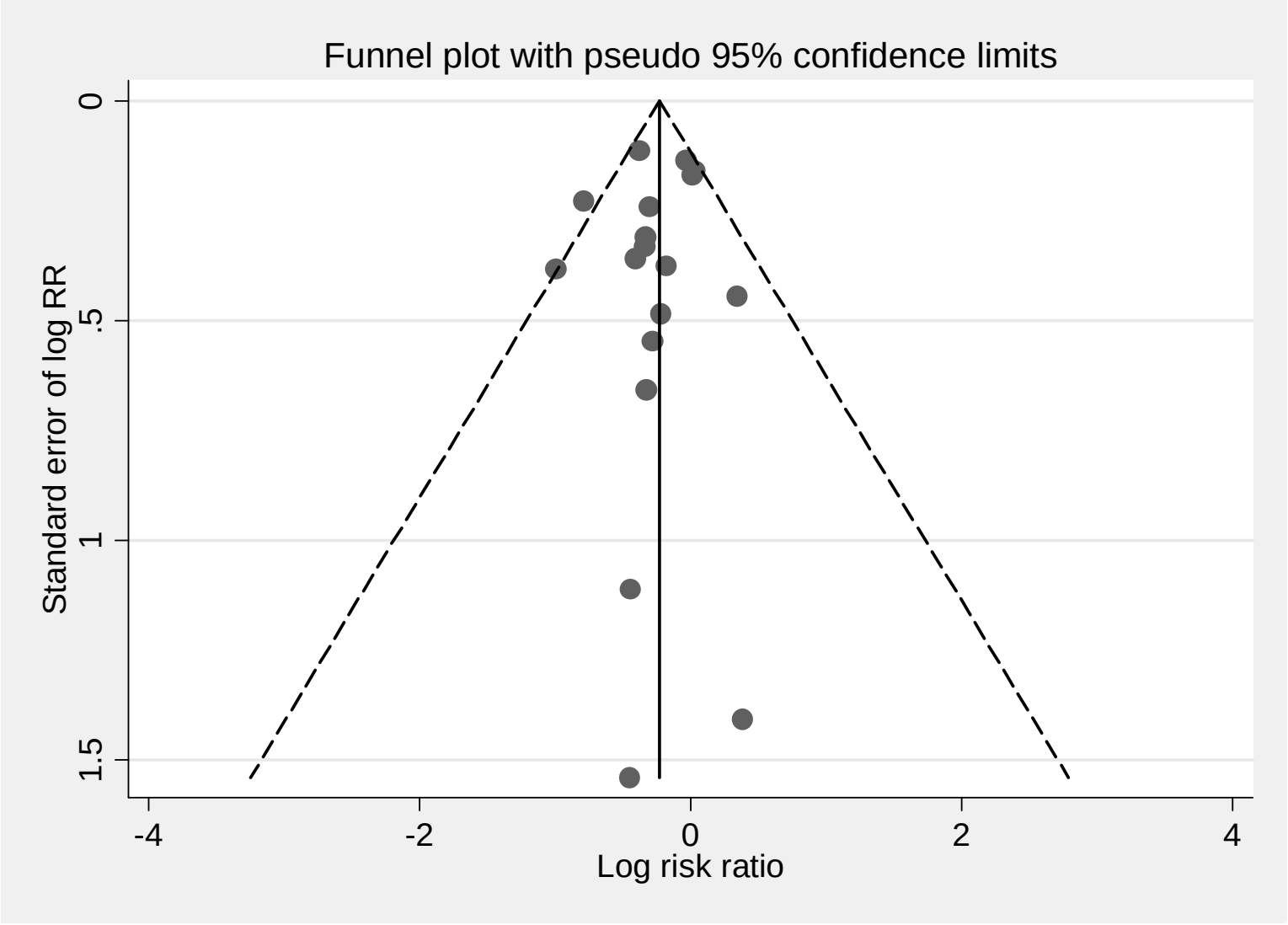
Online Table 2: Total number of patients and events in each group for the primary end-point of the study.

IR Events death
4
6
16
16
73
23
39
16
29
152
372
44
46
179
75
26
32
34
47
51
3
1664
551
30
33
52
24
2
41
3
6
296
817
7
108
107
1105
62
14

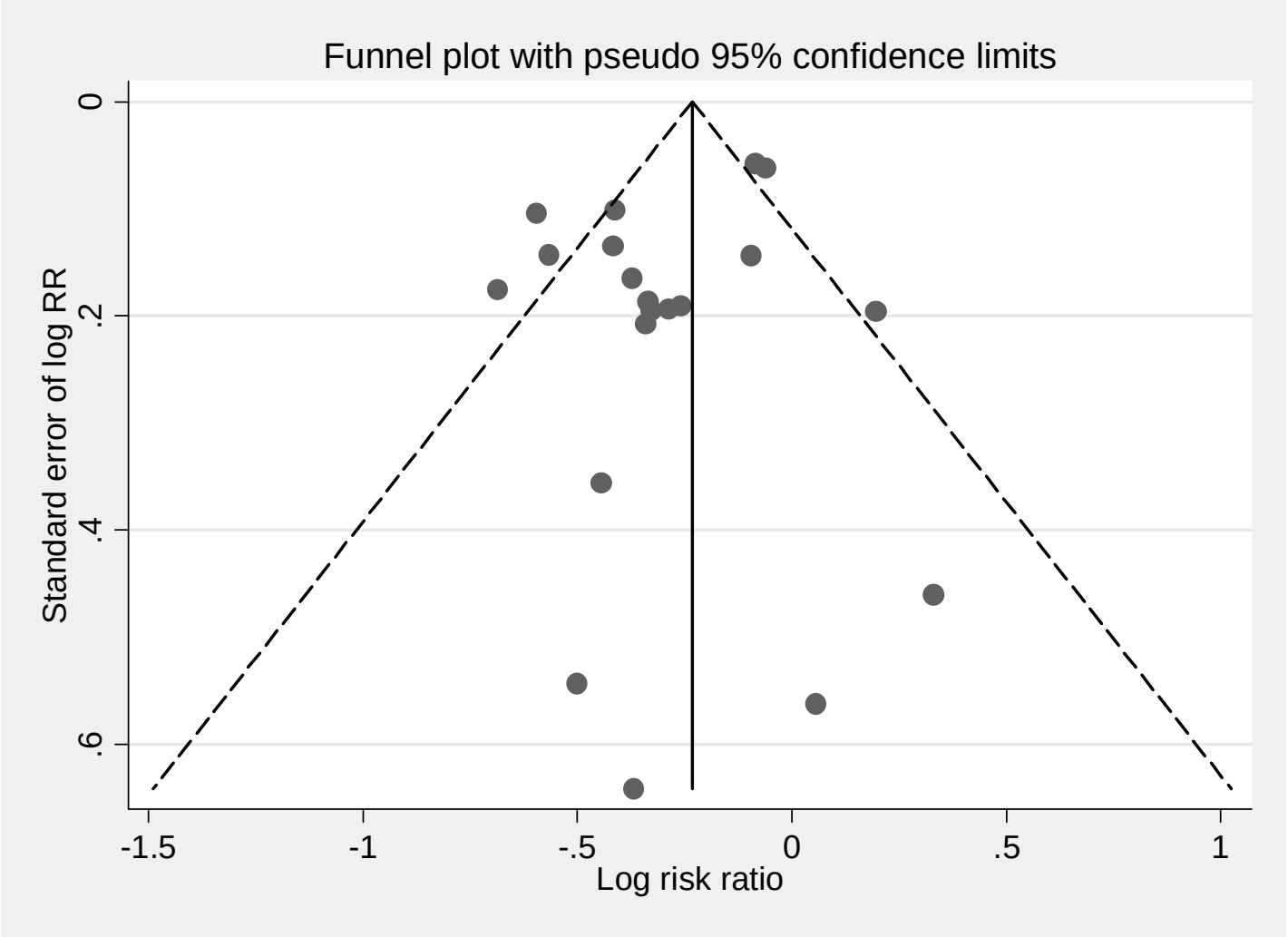
Assessment of publication bias through visual inspection of funnel plot with pseudo 95% confidence limits for the end-point of mortality



Assessment of publication bias through visual inspection of funnel plot with pseudo 95% confidence limits for the end-point of myocardial infarction



Assessment of publication bias through visual inspection of funnel plot with pseudo 95% confidence limits for the end-point of repeat revascularizat



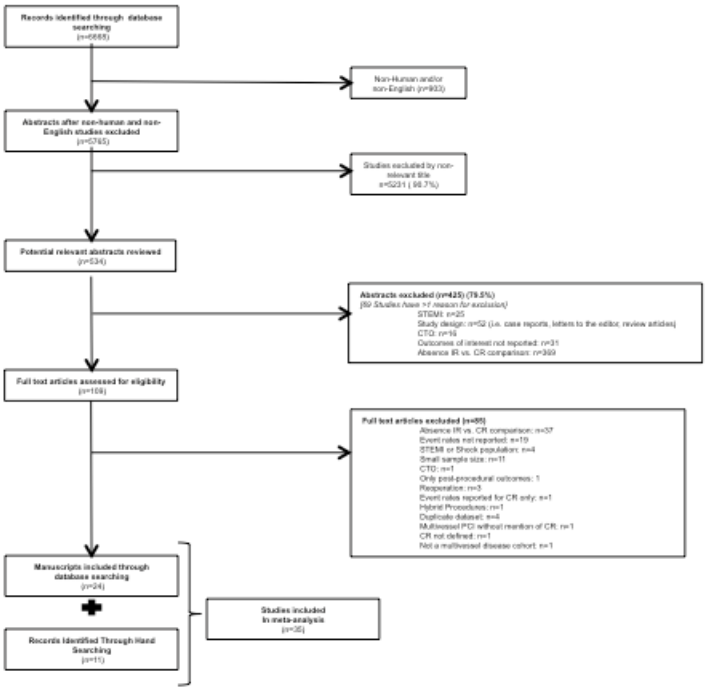


Figure 1

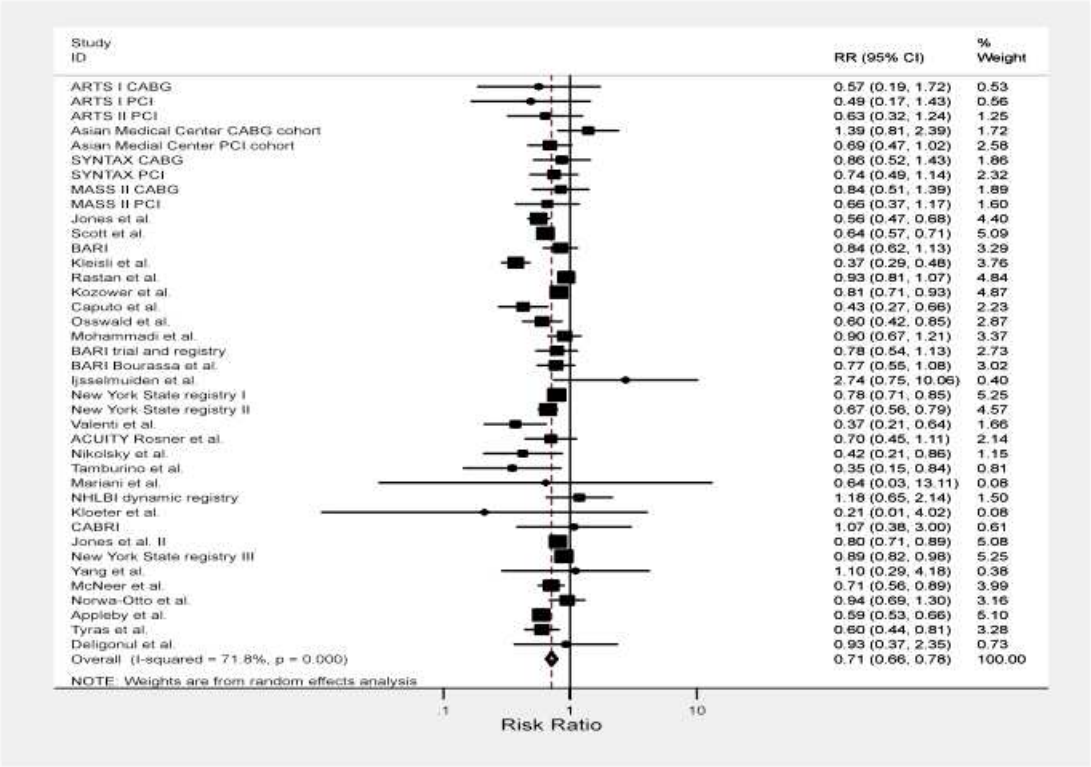
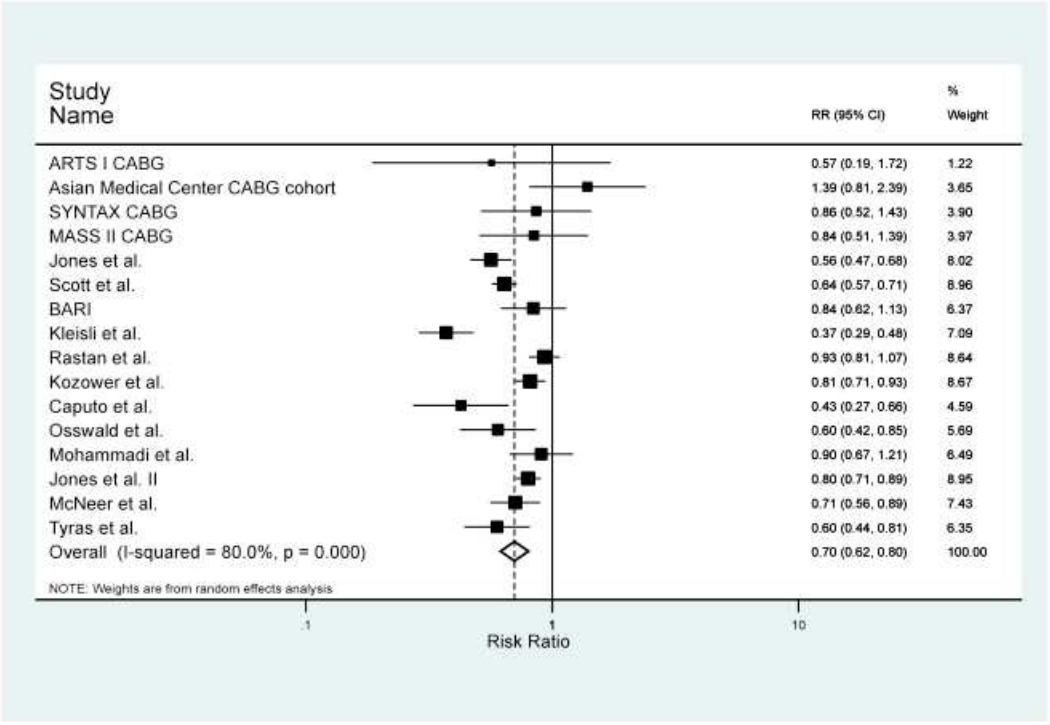


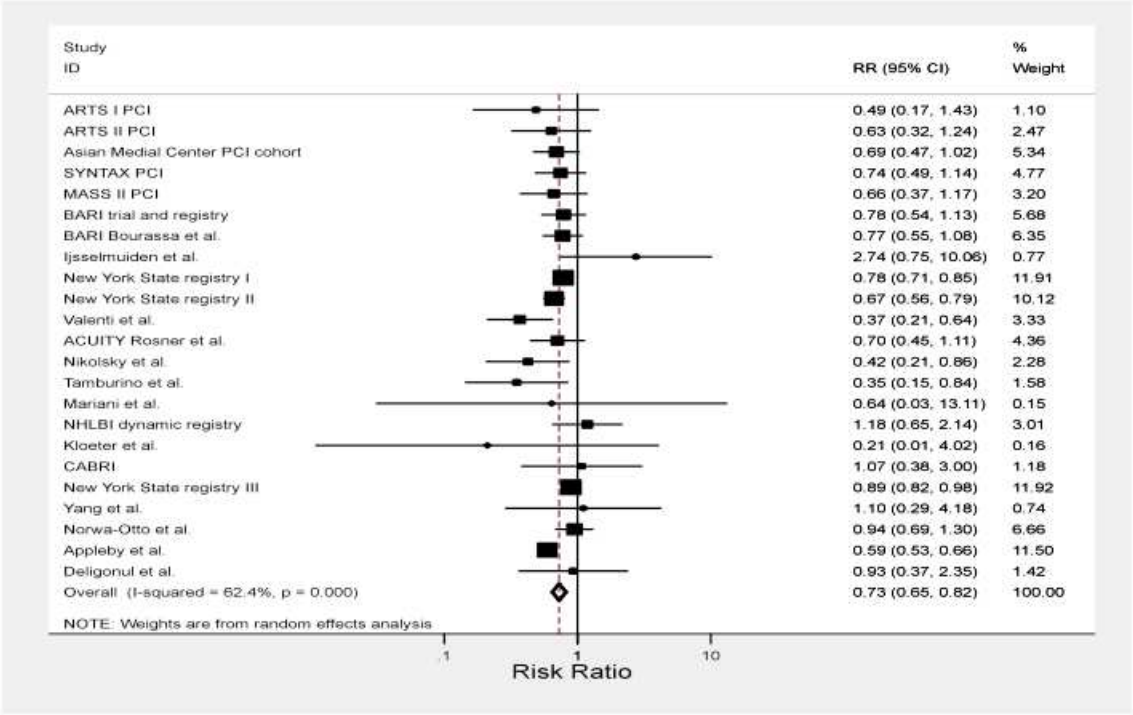
Figure 2



Favors CR

Favors IR

Figure 3



Favors CR Favors IR

Figure 4

Table 1. Summary of Key Demographics Characteristics of Observational Studies and Randomized Clinical Trials Included in this Meta-Analysis

Study Name /First Author	Revascularization Modality	Study Period	Study Design	Definition of CR used	Follow-up (years)	ACS (%) *	Prevalence of IR (%)	Male gender (%)	Mean Age (years)
ARTS I CABG/van der Brand	CABG	1997-1998	Post hoc Analysis of RCT CABG vs. PCI	Anatomical	1	36-39	16	69	61
ARTS I PCI/ van der Brand	PCI	1997-1999	Post hoc Analysis of RCT CABG vs. PCI	Anatomical	1	36-40	30	79	61-62
ARTS II PCI/ Sarno	PCI	2003-2004	Post hoc analysis of nonrandomized clinical trial	Anatomical	5	41-49	39	77	62-63
Asian Medical Center/Kim CABG cohort	CABG	2003-2005	Observational cohort study CABG vs. PCI	Anatomical	5	61	33	72	62-62
Asian Medial Center/ Kim PCI cohort (1)	PCI	2003-2005	Observational cohort study CABG vs. PCI	Anatomical	5	42	59	71	60-62
SYNTAX CABG/Head	CABG	2005-2007	Post hoc analysis of RCT CABG vs. PCI	Anatomical	3	26-32	37	79	64-65
SYNTAX PCI/ Head	PCI	2005-2007	Post hoc analysis of RCT CABG vs. PCI	Anatomical	3	27-30	43	79	65
MASS II CABG/ D'Oliveira Vieira	CABG	1995-2001	Post hoc analysis of RCT CABG vs. PCI	Anatomical	10	0	36	72	62
MASS II PCI/ D'Oliveira Vieira	PCI	1995-2001	Post hoc analysis of RCT CABG vs. PCI	Anatomical	10	0	64	Tab	59
Emory/Jones	CABG	1978-1981	Observational cohort CABG study	Anatomical	5	63	27	84	54
Cleveland /Scott	CABG	1971-1997	Observational cohort CABG study	Anatomical	20	NR	38	81	54
BARI/ Van der Salm	CABG	1988-1991	Post hoc analysis of RCT CABG vs. PCI and observational cohort CABG study	Multiple Definitions **	7	65	17	74	62
Cedars Sinai/Kleisli	CABG	1998-2000	Observational cohort CABG study	Functional	5	NR	9	63	71
Leipzig/Rastan	CABG	2000-2007	Observational cohort CABG study	Anatomical	5	NR	10	77	67
Wash U/Kozower (2)	CABG	1986-2003	Observational cohort CABG study	Anatomical	8	30-34	20	52	83
Bristol Heart Institute/Caputo (3)	CABG	1996-2002	Observational cohort CABG study	Numerical	2	NR	16	75	NR
University of Heidelberg/ Osswald (2)	CABG	1988-1999	Observational cohort CABG study	Anatomical	0.5	NR	16	65	77
Quebec Heart and Lung University Institute/ Mohammadi (2)	CABG	1992-2008	Observational cohort CABG study	Anatomical	8	33-40	18	59	82
BARI trial and registry/ Kip (4)	PCI	1988-1991	Post hoc Analysis of RCT CABG vs. PCI plus registry	Anatomical	5	NR	41	NR	61
BARI/ Bourassa	PCI	1988-1991	Post hoc Analysis of RCT CABG vs. PCI	Anatomical	5	63	36	77	62
Erasmus University/ Ijsselmuiden	PCI	1995-1998	Single center RCT	Anatomical	5	37	50 (randomized)	74	62
New York State registry/ Hannan (5)	PCI	1997-2000	Observational cohort PCI study	Anatomical	3	NR	69	69	NR
New York State registry/ Hannan (5)	PCI	2003-2004	Observational cohort PCI study	Anatomical	1.5	37	69	67	NR
Careggi Hospital/ Valenti (6)	PCI	2003-2006	Observational cohort PCI study	Anatomical	2	32-39	38	83	67-69
ACUITY/ Genereux (7)	PCI	2003-2005	Observational cohort PCI study	Score-based	1	100	60	68	59-63
ACUITY/ Rosner (8)	PCI	2003-2005	Observational cohort PCI study	Anatomical	1	100	37	69	59-61
Nikolsky (9)	PCI	1992-1999	Observational cohort PCI study	Anatomical	3	22	73	73	61
University of Catania/ Tamburino	PCI	2002-2005	Observational cohort PCI study	Anatomical	3	45-55	58	79	61-63
Legnano Italy/ Mariani	PCI	1997-1998	Observational cohort PCI study	Anatomical	1	100	76	83	63
NHLBI dynamic registry/ Srinivas (10)	PCI	1997-2004	Observational cohort PCI study	Anatomical	1	34-39	78	67	61-63
Basel University Hospital/ Kloeter	PCI	1993-1997	Observational cohort PCI study	Anatomical	2.5	NR	40	82	59
CABRI / Breeman (11)	PCI	1990- 1994	Post-hoc analysis of RCT	Anatomical	1	25	72	81	61
Emory/Jones	CABG	1978-1981	Observational cohort CABG study	Anatomical	11	52-56	28	84	57
New York State/Wu (12)	PCI	1999-2000	Observational cohort PCI study	Anatomical	8	NR	70	69	NR
Henan Province/Yang	PCI	2003-2006	Observational cohort PCI study	Anatomical	1.5	92	78	78	61
Duke/McNeer	CABG	1969-1973	Observational cohort CABG study	Numerical	2	NR	52	NR	NR
Warsaw Institute of Cardiology/ Norwa-Otto	PCI	1988-1997	Observational cohort PCI study	Functional	11	30- 36	69	82	52
University of Toronto/ Appleby	PCI	2000-2007	Observational cohort PCI study	Anatomical	3.7	53	65	72	63
Saint Louis University/ Tyras	CABG	1970-1977	Observational cohort CABG study	Anatomical	4	10	29	85	52
Saint Louis University/ Deligonul	PCI	1983-1986	Observational PCI cohort study	Anatomical	2	49	31	76	NR

Table 1. Summary of Key Demographics Characteristics of Observational Studies and Randomized Clinical Trials Included in this Meta-Analysis

Acronyms and Abbreviations:
ARTS: Arterial Revascularization Therapies Study
SYNTAX: Synergy Between PCI with TAXUS and Cardiac Surgery
MASS II: Second Medicine, Angioplasty or Surgery Study
BARI: Bypass Angioplasty Revascularization Investigation
ACUITY: Acute Catheterization and Urgent Intervention Triage Strategy
NHLBI: National Heart, Lung, and Blood Institute
CABRI: Coronary Angioplasty versus Bypass Revascularization Investigation
CABG: Coronary Artery Bypass Surgery
PCI: Percutaneous coronary intervention
ACS: Acute coronary syndrome
NR: Not reported
RCT: Randomized clinical trial