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Revascularization Versus Medical Therapy for the Treatment of Stable Coronary Artery Disease: A Meta-Analysis of Contemporary Randomized Controlled Trials

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ABSTRACT

Background: We conducted a systematic review and meta-analysis of contemporary randomized controlled trials (RCTs) to compare clinical outcomes among stable coronary artery disease (CAD) patients treated with revascularization [percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG) or both] plus medical therapy (MT) or MT alone.

Methods: Prospective RCTs were sought from MEDLINE, Embase, The Cochrane Library, and Web of Science up to April 2020. Data was extracted on study characteristics, methods, and outcomes. Relative risks (RRs) with 95% confidence intervals (CIs) were pooled for the composite of all-cause mortality, myocardial infarction (MI), revascularizations, rehospitalizations, or stroke; its individual components and other cardiovascular endpoints.

Results: Twelve unique RCTs comprising of 15,774 patients were included. There was no significant difference in all-cause mortality risk (0.95, 95% CI: 0.86-1.06); however, revascularization plus MT reduced the risk of the composite outcome of all-cause mortality, MI, revascularizations, rehospitalizations, or stroke (0.69, 95% CI: 0.55-0.87); unplanned revascularization (0.53, 95% CI: 0.40-0.71); and fatal MI (0.65, 95% CI: 0.49-0.84). Revascularization plus MT reduced the risk of stroke at 1 year (0.44, 95% CI: 0.30-0.65) and unplanned revascularization and the composite outcome of all-cause mortality, MI, revascularizations, rehospitalizations, or stroke at 2-5 years.

Conclusions: Revascularization plus MT does not confer survival advantage beyond that of MT among patients with stable CAD. However, revascularization plus MT may reduce the overall risk of the combined outcome of mortality, MI, revascularizations, rehospitalizations, or stroke, which could be driven by a decrease in the risk of unplanned revascularizations, fatal MI or stroke.

Keywords: revascularization; percutaneous coronary intervention; coronary-artery bypass grafting; medical therapy; coronary artery disease; meta-analysis

1.Introduction

Cardiovascular disease (CVD) is known to be the leading cause of death and disability globally and coronary artery disease (CAD) is its main manifestation.[1] Patients with stable CAD have an increased risk of CVD death, myocardial infarction (MI), and stroke,[2] hence the main treatment goals for such stable CAD patients are to reduce the risk of death and MI and also improve their quality of life with the best possible therapies.[3-5] Treatment strategies for stable CAD include medical therapy (MT) and risk factor modification and two forms of revascularization - percutaneous coronary intervention (PCI) and coronary-artery bypass grafting (CABG). Large ischemic myocardial areas may confer an increased risk of death or MI in patients with stable CAD; thus it is used as a criterion in the selection of patients for revascularization procedures.[6]

In patients with acute coronary syndromes (ACSs), both revascularization treatment options (PCI or CABG) are known to increase survival and reduce the risk of nonfatal MI.[7-9] However, the optimal management strategy and implementation of any available invasive intervention for the treatment of the scenario of stable CAD remains controversial. The state of art MT, which includes lifestyle intervention and disease-modifying secondary prevention therapies, such as 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors (statins), renin-angiotensin system inhibitors, antithrombotic agents, such as aspirin (or P2Y12 inhibitors) as well as symptom control agents (e.g., calcium channel blockers, and nitrates), is the foundation of treatment ,which is known to improve clinical outcomes and prognosis in stable CAD.[10, 11] PCI has commonly been used as the invasive treatment of choice in patients with stable CAD, but whether this approach is superior to MT in reducing the risk of death and MI in these patients is still unclear.[10, 12] Several individual randomized controlled trials (RCTs) as well as their pooled analyses have consistently demonstrated no differences in the risk of major outcomes, such as death or MI, between the PCI and MT.[13-16] A limitation of previous meta-analyses is the inclusion of RCTs that did not use contemporary pharmacologic therapies that have been shown to favorably affect prognosis, including aspirin, statins, and renin-angiotensin-aldosterone system inhibitors. Though the evidence suggests CABG might be more effective in comparison to PCI among patients with extensive and prognostically severe CAD, only a very few studies have evaluated the combination of PCI and CABG in comparison to MT in the treatment of stable CAD. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial which assigned patients with both type 2 diabetes and stable CAD to undergo either prompt revascularization (PCI or CABG) with intensive MT or intensive MT alone and to undergo either insulin-sensitization or insulin-provision therapy, no significant differences were found in the rates of death and major CVD events between patients undergoing revascularization and those undergoing MT.[17] In recently published findings of the International Study of Comparative Health Effectiveness

with Medical and Invasive Approaches (ISCHEMIA) trial, the authors did not find evidence that revascularization (PCI or CABG) as compared with MT reduced the risk of ischemic CVD events or death from any cause over a median of 3.2 years in patients with stable CAD.[18]

There has been no previous synthesis of evidence on the clinical effectiveness of revascularization (PCI, CABG or both) plus MT compared with MT alone in the treatment of patients with stable CAD. In this context, we conducted a systemic review and meta-analysis of contemporary RCTs to evaluate whether clinical outcomes are better in those who receive revascularization (PCI or CABG) plus MT than in those who receive MT alone.

2. Methodology

2.1. Data sources and search strategy

A predefined protocol was used in the conduct of this review and was also reported in accordance with PRISMA guidelines (**Appendix 1**).[12] Study authors searched MEDLINE, Embase and The Cochrane library for published studies from inception to 10 April 2020. The computer-based searches combined terms related to the interventions (e.g., "percutaneous coronary intervention" OR "coronary-artery bypass grafting" OR "medical therapy") and population (e.g., "coronary artery disease"). A filter for RCTs was applied. No language restrictions were applied and studies were limited to humans. The detailed search strategy is reported in **Appendix 2**. Following retrieval of article citations, the titles and abstracts were initially screened for potential eligibility. After selection of potential eligible articles, their full texts were acquired for further evaluation. Reference lists of relevant articles were manually scanned to identify potential articles missed by the initial search. Additionally, the "Cited Reference Search" function in Web of Science was used to check for eligible studies missed by the search.

2.2. Study selection and eligibility criteria

We sought prospective RCTs that compared the clinical effectiveness and safety of revascularization (PCI, CABG or both) plus MT or MT alone for treatment of patients with stable CAD. Studies were eligible for inclusion if they (i) assessed the effects of revascularization (PCI, CABG or both) plus MT versus MT alone in randomized patients; (ii) enrolled patients with stable CAD; and (ii) reported outcomes such as the composite of mortality, MI, revascularizations, rehospitalizations, or stroke; all-cause mortality; nonfatal MI; unplanned revascularization; or other CVD endpoints. For studies in which MT was compared with PCI, CABG and PCI plus CABG, the comparisons of MT vs PCI plus CABG were considered. To reflect contemporary practice, we only included RCTs that used stents in their PCI procedures and state of the art MT, such as antithrombotic and statin medications, as part of MT. Trials that

randomized patients with recent ACSs were not included to exclude unstable patients; however, studies of haemodynamically stable patients following a completed MI were included.

2.3. Data extraction, outcomes and assessment of risk of bias

A data extraction form predesigned for this purpose was used to extract information on patient characteristics (e.g., average age, sex, percentage of males); location of study; number of patients enrolled and randomized; study design characteristics, such as randomization, allocation concealment, and blinding; and outcomes, their specific time-points; and risk ratios. Our primary outcomes for this evaluation were (i) the composite of all-cause mortality, MI, revascularizations, rehospitalizations, or stroke; (ii) all-cause mortality; and (iii) MI. Secondary outcomes included were the individual components of the composite primary outcome and other CVD endpoints. Endpoint definitions employed those reported by the individual trials. In instances where information was unavailable from a published report, we collected relevant data by extracting from previously published reviews. Risk of bias for each study was assessed using the Cochrane Collaboration's Risk of Bias tool.[13]

2.4. Statistical analyses

Summary measures of effect were reported as relative risks (RRs) with 95% confidence intervals (CIs), as majority of the trials reported these effect measures. For those that reported counts, RRs with their 95% CIs were estimated. For the few studies that reported HRs, these were assumed to approximate the same measure of RR on the assumption that the outcome is relatively rare at end of follow-up period. For the primary analyses, risk ratios for the longest follow-up were used for each outcome. Subsidiary analyses employed risk ratios for specific time points which were categorised into: short-term (≤ 1 year), intermediate (>1 to 5 years) and long-term (> 5 years). To minimise the effect of between-study heterogeneity, the inverse variance weighted method was used to combine summary measures using random-effects models.(25) We quantified between study statistical heterogeneity using the Cochrane χ^2 statistic and the I^2 statistic.[14] Study-level characteristics including year of enrolment (before 2000 vs after 2000), type of population (stable CAD vs stable after recent MI), design characteristics (eg, allocation concealment, outcome assessment blinding), PCI type (fractional flow reserve-guided (FFR-guided) vs none), type of stent (drug eluting stents (DES) vs bare-metal stent (BMS)) and average duration of follow-up, were evaluated to determine sources of heterogeneity using stratified analysis and random effects meta-regression.[19] Funnel plots and Egger's regression symmetry tests were used to assess for publication bias or small study effects.[20] Subgroup analysis and assessment

of publication bias were conducted for pooled analysis involving 10 or more studies. STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

3. Results

3.1. Study identification and selection

Our search of the databases and scanning of reference lists of relevant articles retrieved 928 potentially relevant citations. After screening based on titles and abstracts, 35 articles remained for further evaluation. Following detailed assessments, 20 articles were excluded for the following reasons: (i) reviews (n=10); (ii) comparator not relevant (n=5); (iii) population not relevant (n=3); and (iv) duplicates of an eligible study (n=2). The remaining 15 articles based on 12 unique RCTs met our inclusion criteria and were included in the meta-analysis (**Figure 1**).[10, 16-18, 21-32]

3.2. Study characteristics and risk of bias

Key characteristics of the RCTs included in the review are reported in **Table 1**. Publication years of studies ranged from 2002 to 2020. In aggregate, the trials comprised 15,774 patients (7,842 assigned to revascularization plus MT and 7,932 assigned to MT alone) with stable CAD. All RCTs were prospective, open-label RCTs. Six trials were single country studies conducted in Brazil, Germany, Denmark, UK, France and Japan; and the other six recruited patients from multiple countries in Europe, Asia, and North and South America. The very recently published large-scale ISCHEMIA trial on this topic was conducted in 38 countries.[18] The baseline average age of participants ranged from 57-64 years, with a weighted mean (standard deviation, SD) of 62 (2) years. The average follow-up duration (based on findings from longest follow-up reports) ranged from 1 to 10 years with a weighted mean (SD) of 4.0 (1.6) years. Using the Cochrane Collaboration tool, all 12 trials demonstrated a high risk of bias for blinding of participants and personnel and a low risk for bias for random sequence allocation, incomplete outcome data, and selective reporting. Two trials had a high risk of bias for blinding of outcome assessment (**Appendix 3**).

3.3. Outcomes for overall follow-up

Figure 2 presents the pooled RRs for primary outcomes based on the longest follow-up of all included studies. In pooled analysis of 8 trials, revascularization plus MT reduced the risk of the composite outcome of mortality, MI, revascularizations, rehospitalizations, or stroke compared with MT alone: 0.69 (95% CI 0.55-0.87). There was evidence of substantial heterogeneity between the contributing trials (I^2=85%, 73 to 92%; p<.001).

Comparing revascularization plus MT with MT alone, there was no statistically significant difference in risk of all-cause mortality (12 trials): RR (95% CI) of 0.95 (0.86-1.06) with no evidence of heterogeneity between contributing trials (I^2=0%, 0 to 58%; p=.93). In pooled analysis of 6 trials, the RR (95% CI) of MI comparing revascularization plus MT with MT alone was 0.96 (0.80-1.15) and there was no evidence of substantial heterogeneity between contributing trials (I^2=24%, 0 to 68%; p=.25).

Secondary outcomes are presented in **Figure 3**. Revascularization plus MT reduced the risk of unplanned revascularizations (10 trials) and fatal MI (2 trials): RRs (95% CIs) of 0.53 (0.40-0.71) and 0.65 (0.49-0.84), respectively. There was evidence of substantial heterogeneity between the contributing trials of unplanned revascularization (I^2=82%, 68 to 90%; p<.001), which seemed to be partly explained by year of participant enrolment, whether PCI was FFR-guided or not and whether stent was BMS or DES (**Appendix 4**). Comparing revascularization plus MT with MT alone, there was no statistically significant differences in risk of nonfatal MI (8 trials); stroke (11 trials); angina during follow-up (6 trials); composite of death and nonfatal MI (2 trials); CVD death (3 trials); composite of CVD death or MI (2 trials); heart failure (4 trials); and CVD death (3 trials): RRs (95% CIs) of 0.87 (0.63-1.20); 0.99 (0.69-1.44); 0.76 (0.53-1.09); 1.11 (0.95-1.29); 0.94 (0.48-1.85); 0.73 (0.53-1.01); 1.14 (0.61-2.13); and 0.91 (0.74-1.14) respectively.

3.4. Outcomes for specific time points

Figure 4 presents the pooled RRs for all outcomes at time points up to 1 year for revascularization plus MT compared with MT alone. Revascularization plus MT reduced the risk of stroke (5 trials): RR (95% CIs) of 0.44 (0.30-0.65). Comparing revascularization plus MT with MT alone, there were no statistically significant differences in the risk of the composite outcome of mortality, MI, revascularizations, rehospitalizations, or stroke (3 trials); all-cause mortality (5 trials); nonfatal MI (4 trials); angina during follow-up (3 trials); CVD death (2 trials); and unplanned revascularization (5 trials). Results from single reports showed no significant differences in the risk of MI or heart failure (**Figure 4**).

At follow-up time 2-5 years, revascularization plus MT reduced the risk of the composite outcome of mortality, MI, revascularizations, rehospitalizations, or stroke (5 trials) and unplanned revascularization (7 trials): RRs (95% CIs) of 0.71 (0.55-0.91) and 0.53 (0.40-0.72), respectively (**Appendix 6**). Comparing revascularization plus MT with MT alone, there was no statistically significant differences in the risk of all-cause mortality (9 trials) and other CVD endpoints (**Appendix 6**).

Only one trial reported outcomes at 10 years follow-up; except for a reduced risk of nonfatal MI for revascularization plus MT, there were no significant differences in the risk of all other outcomes when revascularization plus MT was compared with MT alone (**Appendix 7**).[21]

3.5. Subgroup Analyses and Publication Bias

In subgroup analyses for the outcome of all-cause mortality, there was no evidence of effect modification by year of enrolment, type of population, design characteristics, PCI type, type of stent type and average duration of follow-up (**Appendix 5**). Revascularization plus MT substantially reduced the risk of unplanned revascularizations in trials (i) that enrolled patients after year 2000 compared to those enrolled before 2000 (*p*-value for meta-regression = .03); (ii) that employed FFR-guided PCI compared to those not FFR-guided (*p*-value for meta-regression<.001) and (iii) that used DES compared with BMS (**Appendix 4**).

Under visual examination, funnel plots for those analyses that involved ten or more studies (all-cause mortality, unplanned revascularization and stroke) were all symmetrical and Egger's regression tests showed no statistical evidence of publication bias for all analyses (**Appendix 8**).

4. Discussion

Though invasive strategies of revascularization (PCI or CABG) are well known to reduce CVD morbidity and mortality in ACS, whether they lead to an incremental survival advantage beyond that of MT in stable CAD scenarios has remained controversial. In this first meta-analysis of contemporary trials to compare clinical outcomes of revascularization (PCI, CABG or both) plus MT with MT alone in the treatment of patients with stable CAD, there was no difference in the risk of all-cause mortality; however, revascularization plus MT reduced the overall risk of the composite outcome of all-cause mortality, MI, revascularizations, rehospitalizations, or stroke; unplanned revascularization; and fatal MI, which are important clinical end-points There were no significant differences in the risk of other CVD endpoints. In analyses based on specific time points, revascularization plus MT also reduced the risk of the stroke at 1 year and the risk of unplanned revascularizations and the composite outcome of mortality, MI, revascularizations, rehospitalizations, or stroke at 2-5 years. In subgroup analyses, the beneficial effect of revascularization plus MT on unplanned revascularizations was stronger in more recent trials, FFR-guided PCI and the use of DES.

Invasive intervention by PCI or CABG is commonly known to relieve angina symptoms, reduce the need for antianginal drugs, and improve exercise capacity and quality of life compared with a treatment of MT arm only.[5] Available data has indicated a less restrictive indication for revascularization treatment in stable CAD, when revascularization is focussed on angiographic stenoses on large vessels or left main (LM) - CAD causing ischemia, which can be documented during the angiography by intracoronary FFR assessment or using non-invasive imaging modalities before coronary angiography.[6, 18, 24] Secondly, the degree of myocardial ischemia should be sufficiently large to find most suitable patients for the use of PCI or CABG who would benefit more than those stable CAD patients with less than moderate ischemia as it was determined before invasive evaluation.[18] During the last decade, less invasive therapy of PCI instead of CABG for the treatment of multivessel CAD and/or unprotected LM-CAD has largely increased in clinical practice due to an extensive body of favorable evidence from RCTs.[33] Data reported a few years ago from the FAME 2 trial confirmed persistent clinical advantages in stable CAD patients treated with PCI targeting the stenosed with confirmed ischaemia by invasive physiological guidance (i.e. FFR <0.80) plus MT compared to optimal MT only in terms of a lower rate of revascularization and MI .[26] Additionally, a significant reduction in CVD death and MI was found in an analysis including 2400 patients with FFR-guided PCI plus MT vs. MT alone.[6]However, none of previously mentioned single studies or meta-analyses have been able to provide comprehensive data for application in current stable CAD guidelines, due to limited patient populations, changes in invasive and conservative treatment practices over the years; therefore this meta-analysis of RCTs on stable CAD revascularization with MT compared to MT alone was urgently needed.

The results of ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy or Angioplasty in stable angina), randomized placebo-controlled trial of PCI, showed that even in patients with significant coronary stenosis, exercise capacity and symptoms are not improved significantly compared with a placebo intervention (a ‘sham’ group).[34] Consistent with our study analyses, this trial was based on patients with comprehensive MT in both PCI and sham only groups, including optimally adjusted antianginal therapy. The study highlights a significant placebo component of PCI to the clinical effects of invasive interventions, alerting to potential pitfalls of interpreting endpoints. The ISCHEMIA trial showed that stable CAD patients with at least moderate to severe ischemia had significant, durable improvements in angina control and quality of life with an invasive strategy if they had quite severe and regular angina symptoms (daily/weekly).[35] On the other hand, another explanation for the lack of difference in “hard” outcomes, such as all-cause mortality in RCTs with stable and optimally treated CAD

patients, is likely that this population represents a relatively low risk for clinical events and the potential effect of practice patterns that may have led to exclusion of the most symptomatic patients.

Compared to previous meta-analyses with slightly different inclusion criteria in the treatment strategies of stable CAD, the current study has several advantages which deserve mention.[6, 14-16, 36] We included all currently available RCT-based evidence on this clinically meaningful setting and it is the first comprehensive meta-analysis of contemporary trials in stable CAD patients to compare clinical outcomes between both revascularization strategies and MT. To minimise selective reporting, we evaluated a comprehensive panel of all essential outcomes as reported by the individual trials and these were done by their longest available follow-up times and specific time points. We explored for sources of heterogeneity where appropriate based on the number of trials in each pooled analysis and the degree of heterogeneity. Furthermore, we also evaluated for small study bias (publication bias). Limitations included the inconsistent definition of all CVD outcomes across trials (such as the composite outcome of mortality, MI, revascularizations, rehospitalizations, or stroke) and inability to perform detailed subgroup analyses due to the limited number of trials and outcomes in some of the pooled comparisons. The completeness of revascularization by PCI and/or CABG may have also effects on the outcomes, especially need for reinterventions, however, this kind of data was not available. The definition of MT varied across trials, hence representing a potential source of bias. We also acknowledge that the included RCTs did not address the ischemic zone at risk or residual ischemia in the revascularization group, because the detailed data on area of ischemic myocardium were either not reported or assessed in the trials. Revascularization may have been more likely used among stable CAD patient who have diagnosed 3-vessel CAD or proximal LAD stenosis, but this hypothesis could not be tested in our study level meta-analysis or a single RCT. Stable CAD diagnosis was not performed in the same way in all studies. However, this also reflects reality in clinical practice. In our subgroup analysis involving the type of stents, some of studies employed a mixture of DES and BMS; hence, categorization was done on the basis of which stent constituted the higher proportion in each study.

Medication such as the use of antithrombotic drug use may have changed over the years based on the current recommendations, however, the most recent RCTs with state-of-art medication were included in our updated meta-analysis. Data on beneficial lifestyle changes, such as increased physical activity levels (which improves physical fitness) and health dietary patterns, known to be associated with reduced risk of vascular disease[37-40] and are key in the conservative treatment of CAD, were not available. Many earlier studies have randomized patients after angiographic documentation of coronary stenoses,[16, 24] except for the ISCHEMIA trial,[18] which may have had

effect on the randomization process. Finally, only one trial reported findings on long-term follow-up (10 years), which precluded interpretation and may limit comparability of the results between the analyses based on short-, intermediate- and long-term risk.

5. Conclusions

Revascularization plus MT does not confer overall survival advantage beyond that of MT among patients with stable CAD. However, revascularization plus MT may reduce the overall risk of the combined outcome of all-cause mortality, MI, revascularizations, rehospitalizations, or stroke, which could be driven by a decrease in the risk of unplanned revascularizations, fatal MI or stroke. This contemporary meta-analysis underscores the benefits of appropriately adjusted pharmacotherapy for CAD and an invasive strategy, which can more effectively relieve symptoms of severe angina than MT only, is a rational approach at any point of CAD status in time for symptom relief. Among CAD patients with stable angina pectoris, shared clinical decision-making should occur to align therapy with patients' preferences between invasive strategy plus MT compared to MT use only.

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Declaration of competing interest

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Jari A Laukkanen: Conceptualization, Methodology, Writing -original draft, Writing - review & editing, Visualization. **Setor K Kunutsor:** Conceptualization, Methodology, Writing -original draft, Formal Writing - review & editing, Visualization, Formal analysis.

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Figure legends

Figure 1. Study selection process

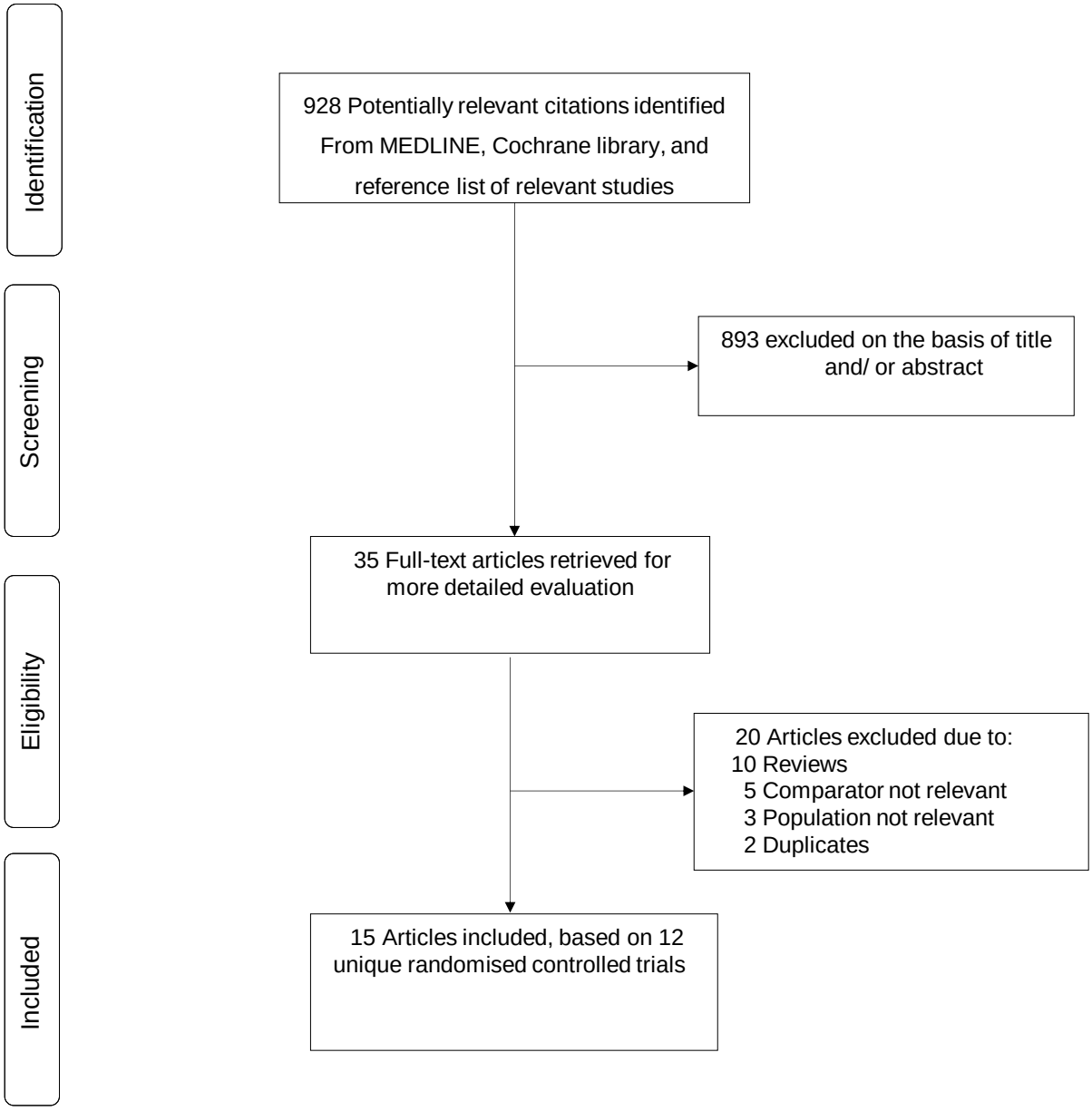
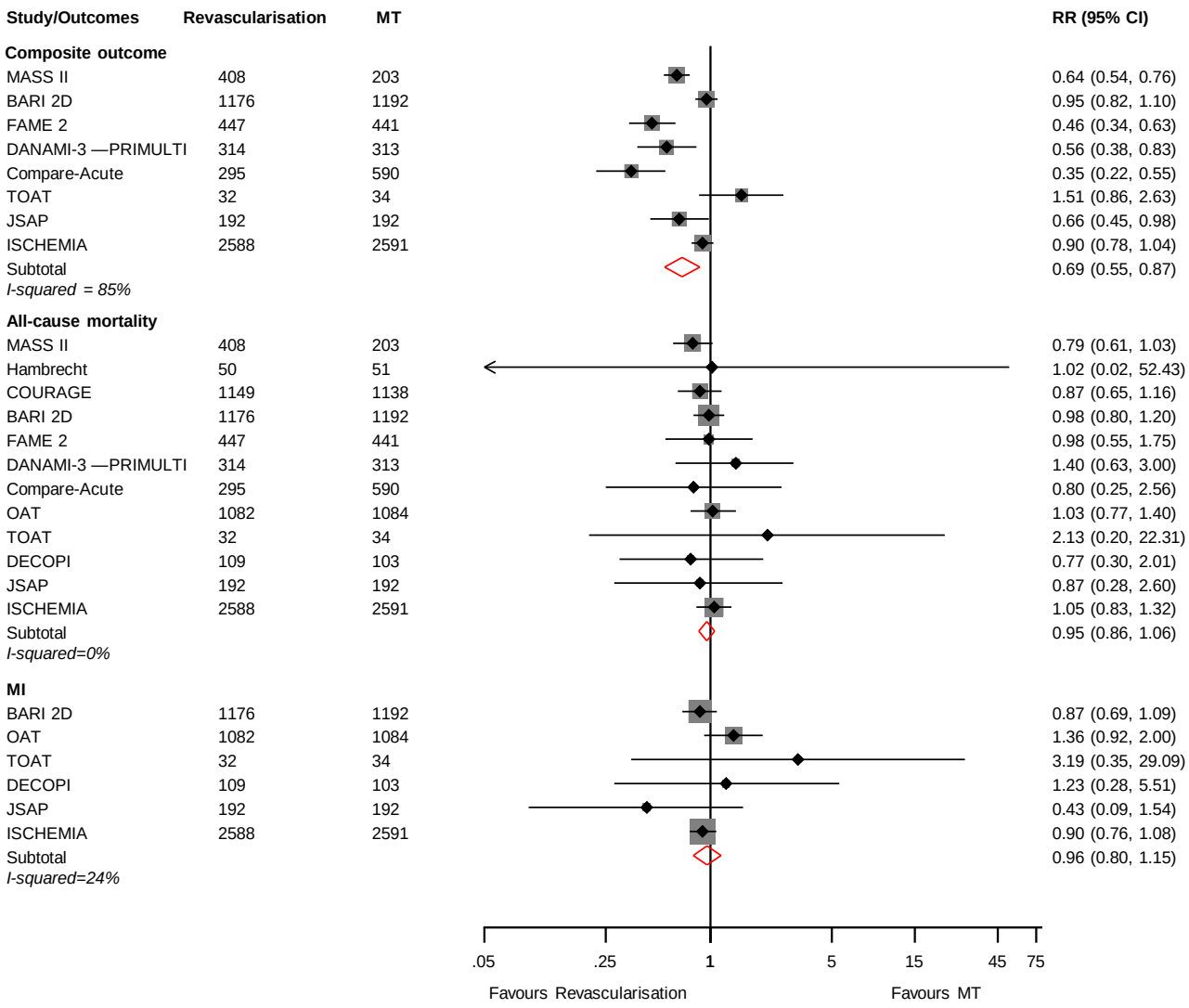


Figure 2. Overall risk of primary outcomes comparing revascularisation plus MT with MT alone

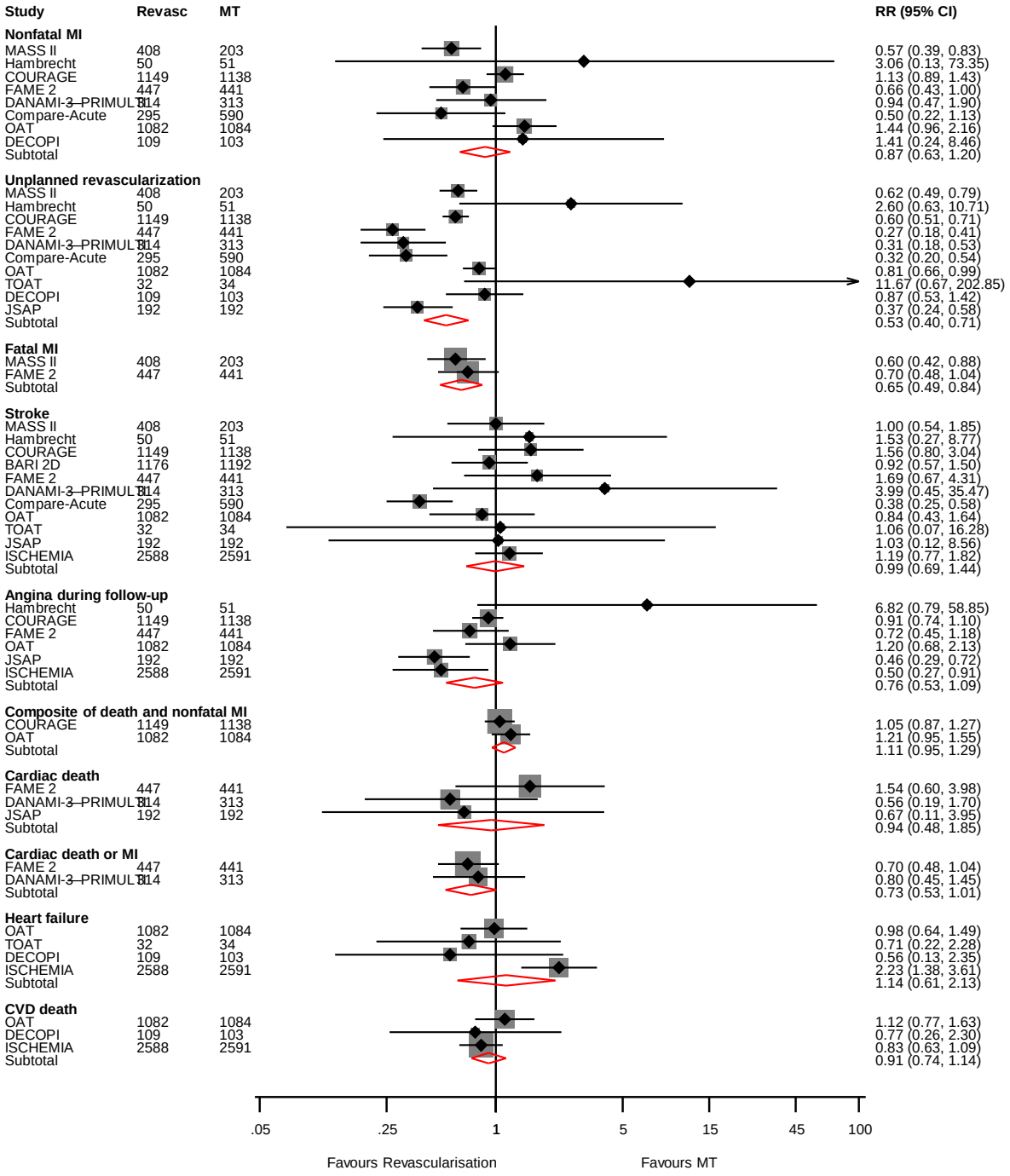


Composite outcome includes all-cause mortality, MI, revascularisation, rehospitalisation, or CVA

CI, confidence interval (bars); CVA, cerebrovascular accident; MI, myocardial infarction; MT, medical therapy; RR, relative risk

Study names in **Table 1** footnotes

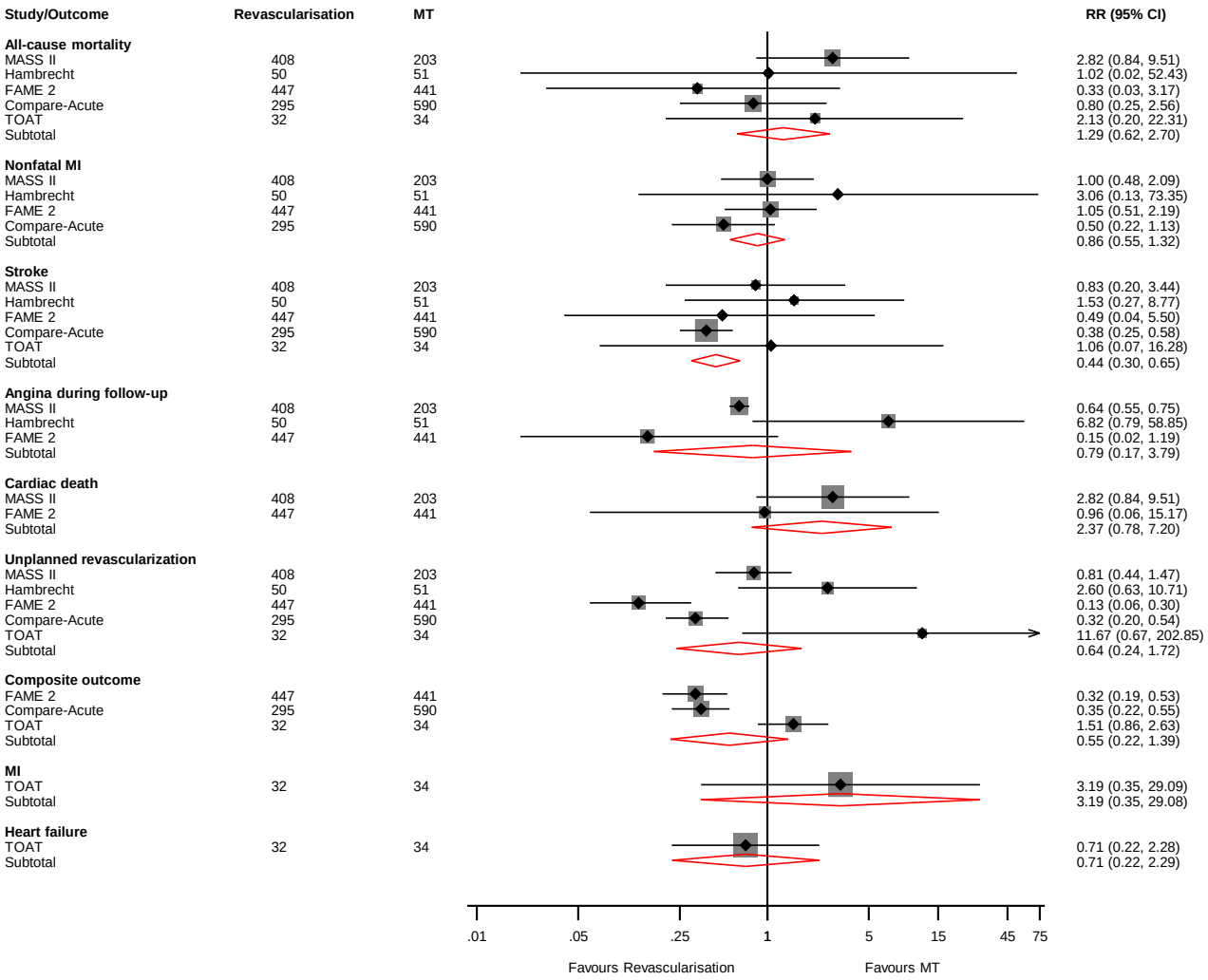
Figure 3. Overall risk of other cardiovascular outcomes comparing revascularization plus MT with MT alone



CI, confidence interval (bars); CVD, cardiovascular disease; MI, myocardial infarction; MT, medical therapy; RR, relative risk

Study names in **Table 1** footnotes

Figure 4. One-year risk of all-cause mortality and cardiovascular outcomes comparing revascularization plus MT with MT alone



Composite outcome includes all-cause mortality, MI, revascularisation, rehospitalisation, or CVA

CI, confidence interval (bars); MI, myocardial infarction; MT, medical therapy; RR, relative risk

Study names in **Table 1** footnotes

SUPPLEMENTARY MATERIAL

Appendix 1	PRISMA checklist
Appendix 2	MEDLINE literature search strategy
Appendix 3	Assessment of risk of bias
Appendix 4	Overall risk of unplanned revascularizations comparing revascularization plus MT with MT alone, grouped by study-level characteristics
Appendix 5	Overall risk of all-cause mortality comparing revascularization plus MT with MT alone, grouped by study-level characteristics
Appendix 6	Two to five years risk of all-cause mortality and cardiovascular outcomes comparing revascularization plus MT with MT alone
Appendix 7	Ten years risk of all-cause mortality and cardiovascular outcomes comparing revascularization plus MT with MT alone
Appendix 8	Assessment of small study effects by funnel plots and Egger's regression symmetry tests

Appendix 1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Title page
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Methods
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Not applicable
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results and Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Results
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results and Figures 2-4; Appendices 4-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Results and Appendix 3
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Results; Appendix 4
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	None

Appendix 2.

MEDLINE literature search strategy 1

1 exp Coronary Disease/ (215381)

2 exp Coronary Artery Disease/ (60666)

3 exp Angina, Stable/ (1283)

4 medical therapy.mp. (26516)

5 exp Percutaneous Coronary Intervention/ (52468)

6 exp Stents/ (76081)

7 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or ("4 arm" or "four arm").ti,ab,kw. (1595088)

8 1 or 2 or 3 (216112)

9 5 or 6 (110569)

10 4 and 7 and 8 and 9 (304)

11 limit 10 to (humans and yr="2012 -Current") (137)

MEDLINE literature search strategy 2

1 exp Coronary Artery Disease/ (60854)

2 exp Coronary Disease/ (215664)

3 exp Angina, Stable/ (1289)

4 exp Coronary Stenosis/ (18340)

5 Myocardial Revascularization/ (10945)

6 exp Coronary Artery Bypass/ (52387)

7 medical therapy.mp. (26578)

8 conservative strategy.mp. (531)

9 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or ("4 arm" or "four arm").ti,ab,kw. (1599803)

10 1 or 2 or 3 or 4 (216399)

11 5 or 6 (61223)

12 7 or 8 (27064)

13 9 and 10 and 11 and 12 (282)

14 limit 13 to humans (282)

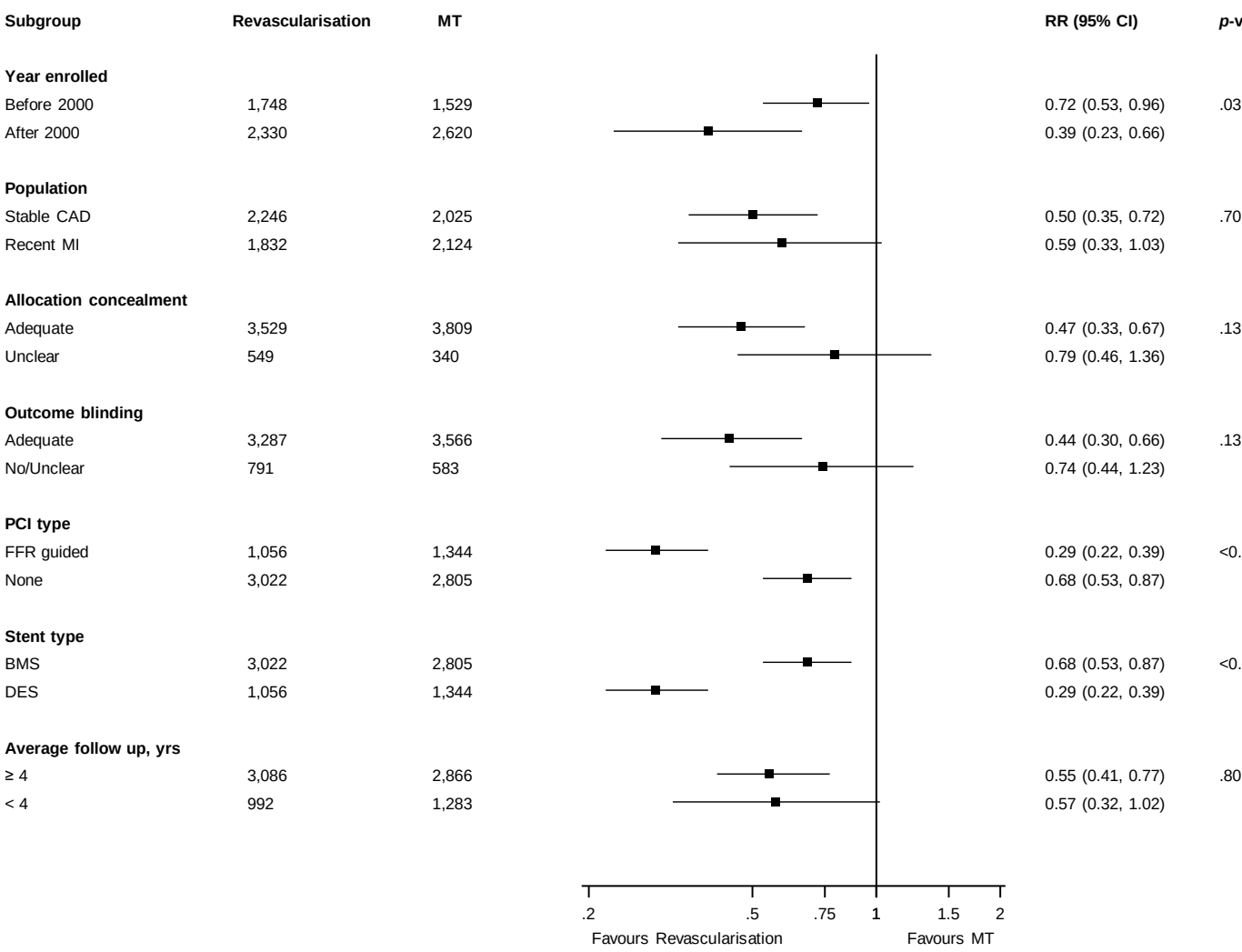
Each part was specifically translated for searching alternative databases.

Appendix 3. Assessment of risk of bias

	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessments*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
MASS II	+	?	-	-	+	+	?
Hambrecht	+	+	-	?	+	+	?
COURAGE	+	+	-	+	+	+	?
BARI 2D	+	+	-	+	+	+	?
FAME 2	+	+	-	+	+	+	?
DANAMI-3—PRIMULTI	+	+	-	+	+	+	?
Compare-Acute	+	+	-	+	+	+	?
OAT	+	+	-	+	+	+	?
TOAT	+	?	-	-	+	+	?
DECOPI	+	?	-	?	+	+	?
JSAP	+	+	-	+	+	+	?
ISCHEMIA	+	+		+	+	+	?

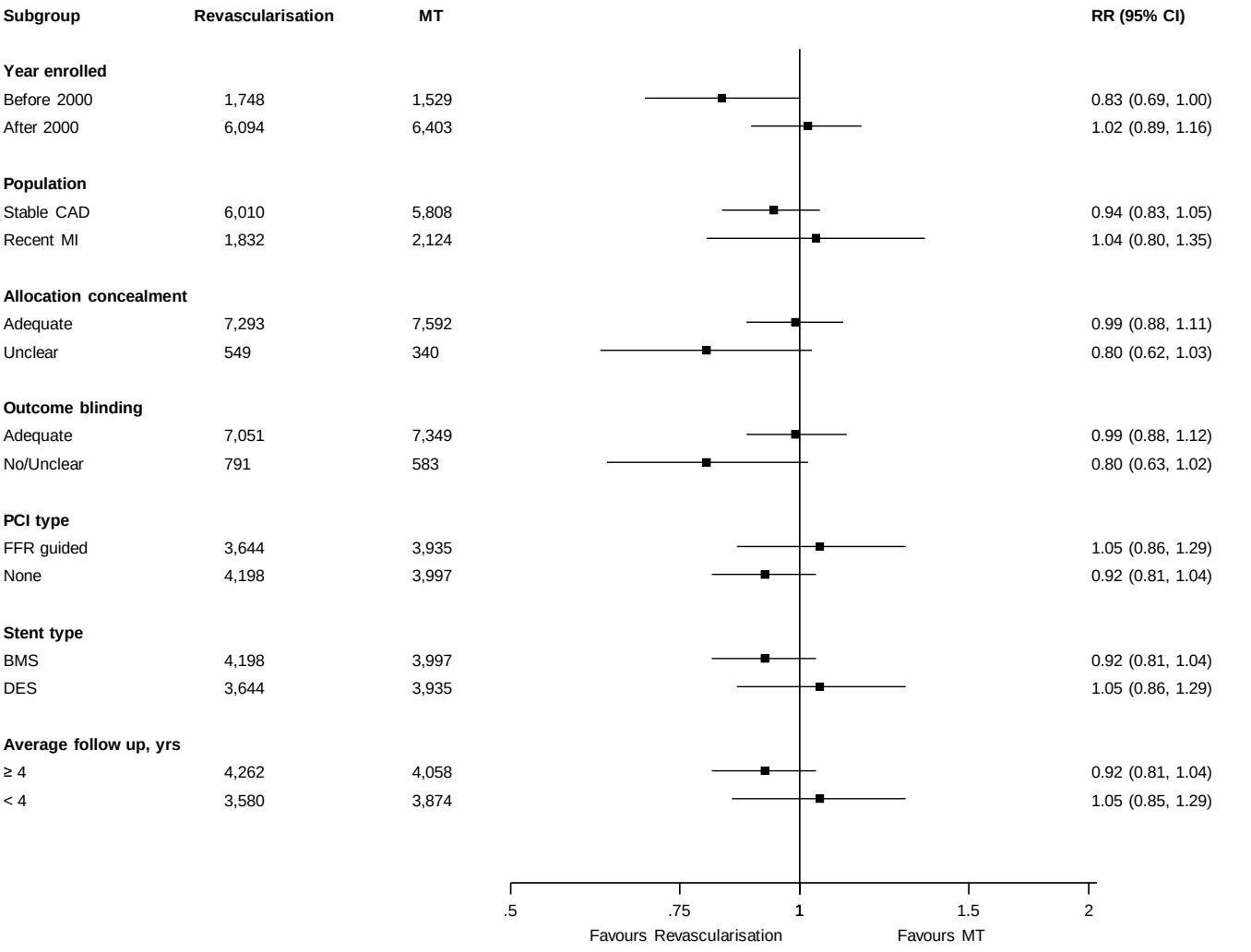
+	**Low risk of bias**
?	**Unclear risk of bias**
-	**High risk of bias**

Appendix 4. Overall risk of unplanned revascularizations comparing revascularization plus MT with MT alone, grouped by study-level characteristics



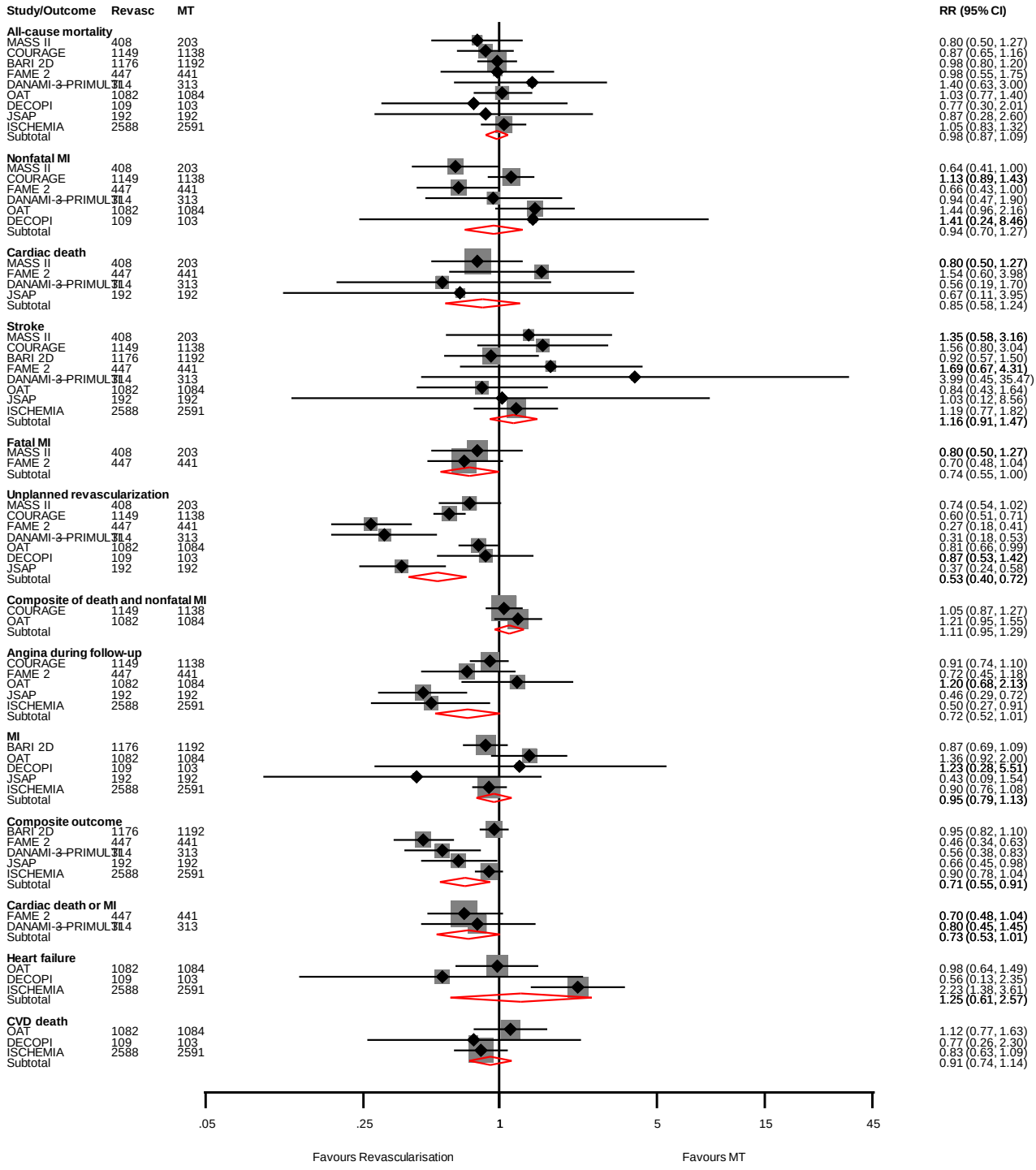
BMS, bare-metal stent; CAD, coronary artery disease; CI, confidence interval (bars); DES, drug eluting stent; FFR-guided, fractional flow reserve-guided; MI, myocardial infarction; RR, relative risk; *p*-value is for meta-regression

Appendix 5. Overall risk of all-cause mortality comparing revascularization plus MT with MT alone, grouped by study-level characteristics



BMS, bare-metal stent; CAD, coronary artery disease; CI, confidence interval (bars); DES, drug eluting stent; FFR-guided, fractional flow reserve-guided; MI, myocardial infarction; RR, relative risk; *p*-value is for meta-regression

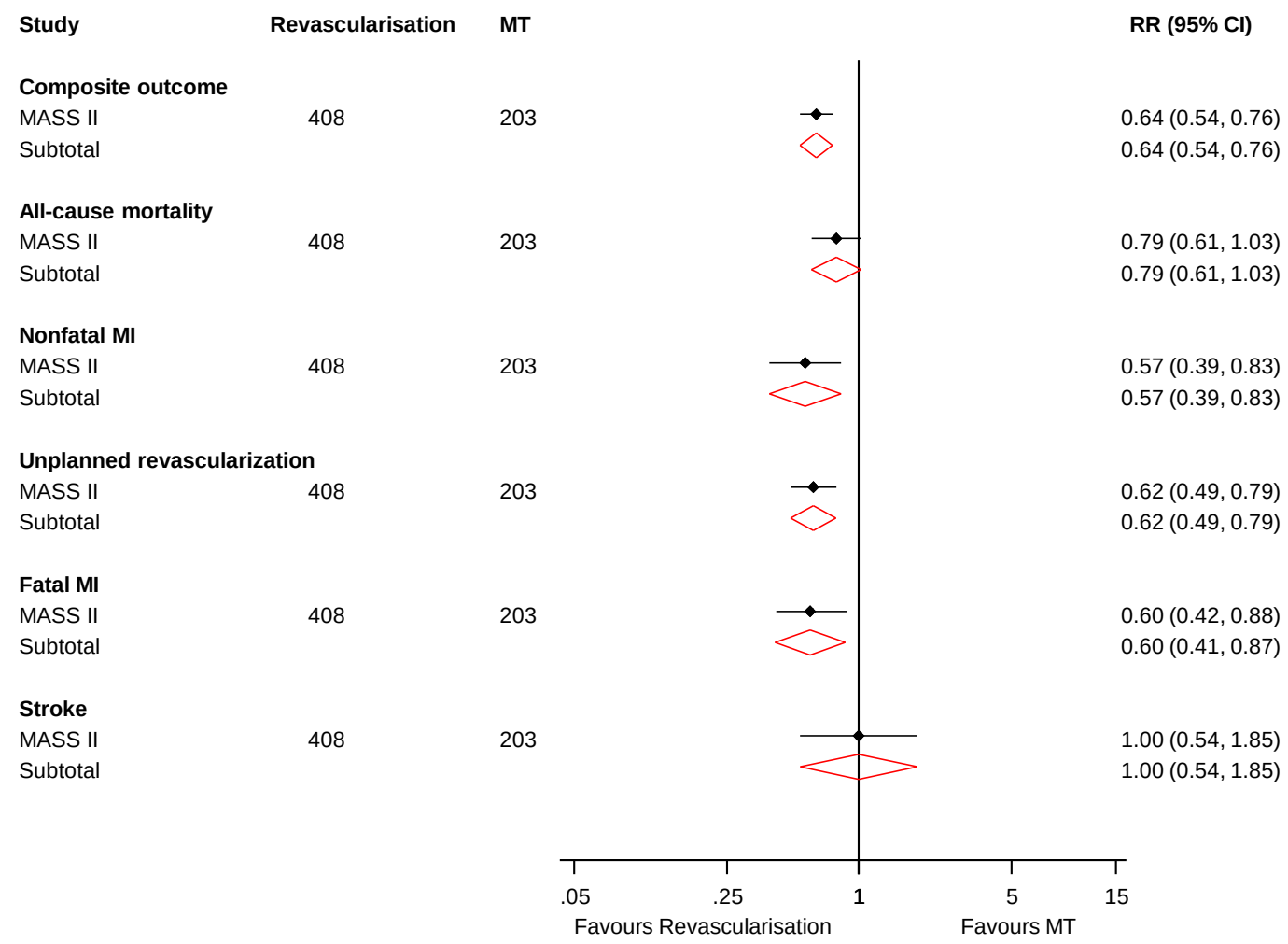
Appendix 6. Two to five years risk of all-cause mortality and cardiovascular outcomes comparing revascularization plus MT with MT alone



Composite outcome includes all-cause mortality, MI, revascularisation, rehospitalisation, or CVA

CI, confidence interval (bars); MI, myocardial infarction; MT, medical therapy; RR, relative risk

Appendix 7. Ten years risk of all-cause mortality and cardiovascular outcomes comparing revascularization plus MT with MT alone

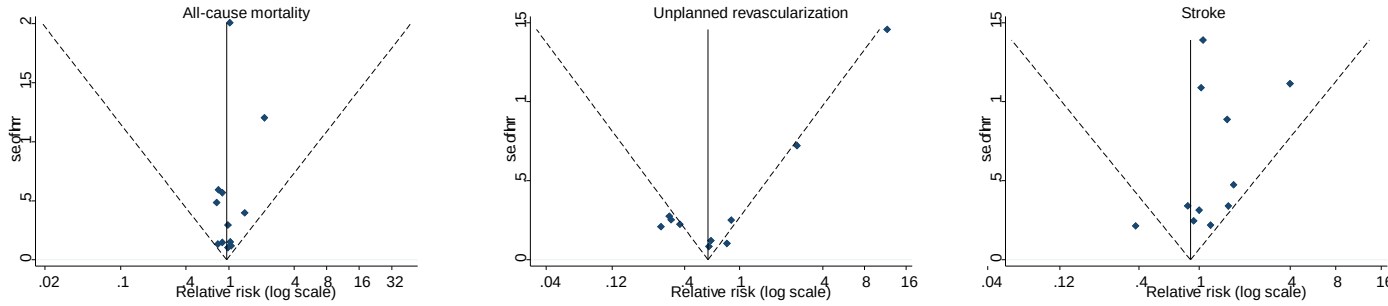


Composite outcome includes all-cause mortality, MI, revascularisation, rehospitalisation, or CVA

CI, confidence interval (bars); CVA, cerebrovascular accident; MI, myocardial infarction; MT, medical therapy; RR, relative risk

Study names in **Table 1** footnotes

Appendix 8. Assessment of small study effects by funnel plots and Egger's regression symmetry tests



The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a fixed effect model; *P*-values for bias calculated using Egger's test were 0.75, 0.76, and 0.20 for all-cause mortality, unplanned revascularization, and stroke

Table 1. Key characteristics of randomized controlled trials

Author, year of publication	Study name/First author	Baseline population	Years of enrolment	Male %	Mean/median age (years)	Location	Stent implantation (%)	Drug-eluting stent (%)	Definition of medical therapy	CABG (%)	Follow-up duration (years)	Total participants	Revascularization plus MT participants	MT alone participants
Yousef, 2002	TOAT	Q-wave anterior MI with persistent occlusion of the LAD and absence of chest pain	1997-1999	80.0	58	UK	100	0	Aspirin, beta-blockers, ACEI and lipid-lowering agents	0.0	1.0	66	32	34
Steg, 2004	DECOPI	Stable patients within 15 d of Q-wave MI, no ischemia, and total occlusion of the infarct-related artery	1998-2001	85.0	57	France	80	0	NA	0.0	3.0	212	109	103
Hueb, 2004, 2007, 2010	MASS II	Angiographically documented proximal multivessel coronary stenosis of >70% by visual assessment and documented ischemia	1997-2001	67.9	60	Brazil	72	0	Nitrates, aspirin, beta-blockers, calcium channel blockers, ACEI, or a combination of these drugs, unless contraindicated. Hydroxymethylglutaryl-coenzyme A reductase inhibitors plus low-fat diet on an individual basis	33.0	1, 5 and 10	611	408	203
Hambrecht, 2004	Hambrecht	Stable CAD and 1 native coronary artery stenosis of ≥75% by visual assessment by PCI	1997-2001	100	61	Germany	100	0	Usual medical therapy with 12 months of exercise training (20 minutes of bicycle ergometry per day)	0.0	1.0	101	50	51
Hochman, 2006	OAT	Stable patients 3 to 28 d after MI with total occlusion of the infarct-related artery	2000-2005	78.0	59	Europe, Asia, North America	87	8	Aspirin, anticoagulation if indicated, ACEI, betablockade, and lipid-lowering therapy	0.0	4.0	2166	1082	1084
Boden, 2007	COURAGE	Stable CAD and CCS class IV angina	1999-2004	85.1	62	USA, Canada	94	2.7	Long acting metoprolol, amlodipine, isosorbide mononitrate, alone or in combination with lisinopril/losartan; simvastatin alone or in combination with ezetimibe; exercise, extended-release niacin, or fibrates, alone or in combination	0.0	4.6	2287	1149	1138
Nishigaki, 2008	JSAP	Stable exertional angina or inducible ischemia; stenosis 75%	2002-2004	75.0	64	Japan	99	0	Antianginal.therapy and drugs for risk factor treatment	0.0	3.3	384	192	192
Frye, 2009	BARI 2D	Type 2 diabetes and CAD documented on angiography	2001-2005	73.0	62	N. and S. America, Europe	91	35	Statins, aspirin, beta-blockers, and ACEI/ ARB	32.1	5.3	2368	1176	1192

De Bruyne, 2012; Xaplanteris, 2018	FAME 2	Stable CAD considered for PCI	2010-2012	78.2	64	Europe and N. America	NA	100	Aspirin, metoprolol (or any other beta-1–selective blocker, alone or in combination with a calcium-channel blocker or a long-acting nitrate), lisinopril, or ACEI/ARB and atorvastatin or another statin of similar potency alone or in combination with ezetimibe	0.0	0.59 and 5	888	447	441
Engstrom, 2015	DANAMI-3—PRIMULTI	ST elevation MI	2011-2014	80.7	63.5	Denmark	NA	95	Antiplatelets, statin, beta blocker, ACEI/ARB, calcium channel blocker	0.0	2.3	627	314	313
Smits, 2017	Compare-Acute	ST elevation MI	2011-2015	77.2	61.3	Europe and Asia	NA	98.8	NA	0.0	1.0	885	295	590
Maron, 2020	ISCHEMIA	Stable CAD and moderate or severe ischemia	2012-2018	77.4	64.0	38 countries	93.0	98.1	Aspirin, statin, ACEI/ARB, beta blocker, P2Y12 receptor antagonist, ezetimibe, evolocumab	26.0	3.2	5179	2588	2591

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary-artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; LAD, left anterior descending; MI, myocardial infarction; MT, medical therapy; NA, not available; PCI, percutaneous coronary intervention

Study Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation; DECOPI, DEsobstruction COronaire en Post-Infarctus; FAME, Fractional Flow Reserve versus Angiography for Multivessel Evaluation; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; JSAP, Japanese Stable Angina Pectoris Study; MASS II, Medicine, Angioplasty, or Surgery Study; OAT, Occluded Artery Trial; TOAT, The Open Artery Trial