Percutaneous Coronary Intervention Versus Optimal Medical Therapy for Prevention of Spontaneous Myocardial Infarction in Subjects With Stable Ischemic Heart Disease

Sripal Bangalore, MD, MHA; Seema Pursnani, MD, MPH; Sunil Kumar, MD; Pantelis G. Bagos, PhD

Background—Contemporary studies have shown that spontaneous but not procedural myocardial infarction (MI) is related to subsequent mortality. Whether percutaneous coronary intervention (PCI) reduces spontaneous (nonprocedural) MI is unknown.

Methods and Results—PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials until October 2012 comparing PCI with optimal medical therapy (OMT) for stable ischemic heart disease and reporting MI outcomes: spontaneous nonprocedural MI, procedural MI, and all MI, including procedure-related MI. Given the varying length of follow-up between trials, a mixed-effect Poisson regression meta-analysis was used. From 12 randomized clinical trials with 37 548 patient-years of follow-up, PCI compared with OMT alone was associated with a significantly lower incident rate ratio (IRR) for spontaneous nonprocedural MI (IRR=0.76; 95% confidence interval [CI], 0.58–0.99) at the risk of a higher rate of procedural MI (IRR=4.11; 95% CI, 2.53–6.88) without any difference in the risk of all MI (IRR=0.96; 95% CI, 0.74–1.21). The point estimate for PCI versus OMT for all-cause mortality (IRR=0.88; 95% CI, 0.75–1.03) and cardiovascular mortality (IRR=0.70; 95% CI, 0.44–1.09) paralleled that for spontaneous nonprocedural MI (but not procedural or all nonfatal MI), although these were not statistically significant.

Conclusions—PCI compared with OMT reduced spontaneous MI at the risk of procedural MI without any difference in all MI. Consistent with prior studies showing that spontaneous MI but not procedural MI is related to subsequent mortality, in the present report the point estimate for reduced mortality with PCI compared with OMT paralleled the prevention of spontaneous MI with PCI. Further studies are needed to determine whether these associations are causal. **(*Circulation*. 2013;127:769-781.)**

Key Words: optimal medical therapy ■ periprocedural myocardial infarction

In numerous prior studies, the occurrence of spontaneous myocardial infarction (MI) (unrelated to revascularization procedures) has been consistently associated with subsequent mortality.[1–3] In contrast, although percutaneous coronary intervention (PCI) may result in procedural complications including MI and, rarely, death, in most contemporary studies such periprocedural MIs have not been associated with subsequent mortality.[2–6] The frequency of procedural MI varies depending on the population studied, the biomarker tested, and the threshold definition used, with frequency ranging up to 50%,[7] and its prognostic significance is controversial.[1,3,6,8] In addition, there is controversy about the threshold of biomarker elevation after PCI that is prognostically significant.[9]

Clinical Perspective on p 781

The objective of the present study was to evaluate the association of PCI compared with optimal medical therapy (OMT) alone with various types of MI: spontaneous nonprocedural MI, procedural MI, and all MI, including procedural MI.

Methods

Eligibility Criteria

We conducted PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) searches for randomized clinical trials (RCTs) until October 2012 (week 2) using the following terms: *coronary artery disease*, *ischemic heart disease*, *angina*, *percutaneous coronary intervention*, *percutaneous transluminal coronary angioplasty*, or *revascularization*. The Medical Subject Headings terms are listed in Table I in the online-only Data Supplement. We checked the reference lists of review articles, meta-analyses, and original studies identified by the electronic searches to find other eligible trials. There was no language restriction for the search. For studies that did not report outcomes of interest, we contacted the authors via e-mail.

Eligible trials had to fulfill the following criteria: (1) RCTs comparing PCI versus OMT in patients with stable coronary artery disease and (2) RCTs reporting outcomes of MI. Trials that enrolled patients within a week of acute coronary syndromes were excluded. For the purpose of this analysis, PCI was defined as percutaneous transluminal coronary angioplasty with or without bare metal or drug-eluting stent placement. The PCI trials were divided into "no-stent" trials, in which <50% of patients in the PCI group received a stent, and "stent" trials, in which ≥50% patients received a stent. In addition, OMT was

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defined as a medical therapy consisting of at least an antiplatelet, antianginal, and lipid-lowering agent. Given the design of this analysis, trials in which revascularization could be achieved by either PCI or coronary artery bypass graft were excluded. However, in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, patients were divided into either a PCI stratum or a coronary artery bypass graft stratum before randomization to revascularization or medical therapy. Only the PCI stratum was included in this analysis, and the medical therapy group from the coronary artery bypass graft stratum was also excluded because these subjects are likely a higher-risk medical therapy group (matched to the coronary artery bypass graft arm) than the medical therapy group in the PCI stratum.

Selection and Quality Assessment

Three authors (S.B., S.P., S.K.) independently assessed trial eligibility and trial bias risk and extracted data. Disagreements were resolved by consensus. The bias risk of trials was assessed with the use of the components recommended by the Cochrane Collaboration[10]: Sequence generation of allocation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias and trials with high or unclear risk for bias for any 1 of the first 3 components were considered trials with high bias risk. Dr Bangalore had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Extraction and Synthesis

Three different nonfatal MI outcomes were evaluated: (1) spontaneous nonprocedural MI; (2) procedural MI; and (3) all MI, including procedure-related MI. Other outcomes evaluated included all-cause mortality and cardiovascular mortality. The longest reported follow-up events were abstracted for each of the trials.

Statistical Analyses

Summary Method

The meta-analysis was performed in accordance with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[10,11] with the use of standard software (Stata 9.0, Stata Corporation, College Station, TX).[12] The analysis used the incident rate of outcomes per 1000 person-years to obtain the log incident rate ratio (IRR) of one treatment relative to another treatment. Rates, rather than number of events, were considered the most appropriate outcome for this analysis because they incorporate the duration of the trials. Patient-years of follow-up were calculated by multiplying the sample size by the mean follow-up duration.

For the summary-based approach, IRR was calculated with the use of the random-effects model of DerSimonian and Laird.[13] All analyses were performed with a random-effects model given likely clinical heterogeneity in study design between trials regardless of statistical heterogeneity. Heterogeneity was assessed with the I^2 statistic,[14] which is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance), with I^2 <25% considered low and I^2 >75% considered high. Analyses were stratified by stent versus no-stent trials. We estimated the difference between the estimates of these subgroups according to tests for interaction.[15] $P_{interaction}<0.10$ indicates that the effects of treatment differ between the tested subgroups. Bias was estimated visually by funnel plots and with the use of the Begg test and the weighted regression test of Egger.[16] $P<0.05$ was used to denote statistical significance.

Mixed-Effect Poisson Regression

A generalized linear mixed model framework with the Poisson likelihood and log-link function approach[17] was used to calculate effect sizes. Formulation of the model for incidence data requires the use of the logarithm of the total number of counts as the dependent variable in a Poisson regression, with the inclusion of the logarithm of the total person-time as an offset (a variable with coefficient constraint to be 1). The treatment is included as an explanatory variable, and random treatment effects are accommodated as random coefficients. To be completely analogous to the summary-based model, the Poisson regression approach requires the inclusion of fixed study-specific intercepts (to preserve stratification).[17]

This particular model directly uses the appropriate likelihood for count data and can be more accurate and powerful particularly when the normality assumptions do not hold for the estimated log IRRs or when there are few studies in the meta-analysis. Moreover, the same model can produce estimates for other relevant measures such as the incidence rate difference.[17] Poisson regression models were fitted in Stata with the use of the generalized linear latent and mixed models module.

Sensitivity Analyses

Sensitivity analysis was performed with the exclusion of trials that clearly included patients without ischemia (Atorvasttin Versus Revascularization Treatment [AVERT], FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses [DEFER]) because it is not clear whether PCI would be beneficial in those subsets. All included studies fared similarly on the risk of bias assessment, and we therefore did not pursue a sensitivity analysis based on quality of trials.

Meta-Regression Analysis

Meta-regression analyses were performed to evaluate the relationship of covariates with all-cause mortality. The following covariates were tested independently to evaluate the relationship with IRR of all-cause mortality: (1) adequacy of PCI as measured by percent stent usage in the PCI arm; (2) adequacy of medical management as evaluated by achieved low-density lipoprotein levels in the OMT arm; and (3) effect of crossovers (defined as percentage of patients in the OMT arm who underwent revascularization). We used residual maximum likelihood to estimate the additive (between-study) component of variance tau^2 for the meta-regression analysis. Bootstrap analyses were performed with the use of a Monte Carlo permutation test for meta-regression with 10 000 random permutations.[18]

Results

Study Selection

We identified 12 RCTs that satisfied our inclusion criteria (Figure 1).[19–34] For the BARI 2D trial, we included the PCI stratum of the trial only. The trials enrolled a total of 8070 patients who were followed up for a mean of 5.0 years (range, 1.5–10.2 years) with 37 548 patient-years of follow-up.

Baseline Characteristics

The baseline characteristics of the included trials are summarized in Tables 1 and 2. In the majority of trials, angioplasty without stenting was performed. In 4 of the 12 RCTs (BARI

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2D trial; Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial; Medicine, Angioplasty, or Surgery Study [MASS II] trial; and Japanese Stable Angina Pectoris Study [JSAP] trial), >50% of patients in the PCI arm received a stent. However, only a small fraction received drug-eluting stents (DES), with the largest being in the BARI 2D, in which a third of patients received a DES (first generation).

The medical therapy varied among trials, but most patients were taking at least a daily low-dose aspirin and were on antianginal therapy with nitrates and β-blockers. For the most part, the medical therapies were used uniformly in both the PCI and medical therapy groups of each of the included trials, with the exception of the Angioplasty Compared to Medicine (ACME)-1 trial, in which all antianginal therapies were discontinued in the PCI group before study entry.

Myocardial Infarction

Spontaneous Nonprocedural MI

PCI compared with OMT alone (event rate, 13.68 versus 17.30 per 1000 patient-years) was associated with a 24% reduction in the IRR of spontaneous nonprocedural MI on the basis of a random-effects Poisson regression model (IRR=0.76; 95% confidence interval [CI], 0.58–0.99) (Figure 2). The results were similar when a summary-based random-effects model was used (IRR=0.77; 95% CI, 0.60–0.99) (Figure 2). There was moderate heterogeneity in the analysis (I^2=31.6%) with no evidence of publication bias (Egger's *P*=0.49; Begg's *P*=0.75) (Figure I in the online-only Data Supplement).The results were similar when no-stent and stent trials were analyzed separately ($P_{interaction}$=0.53).

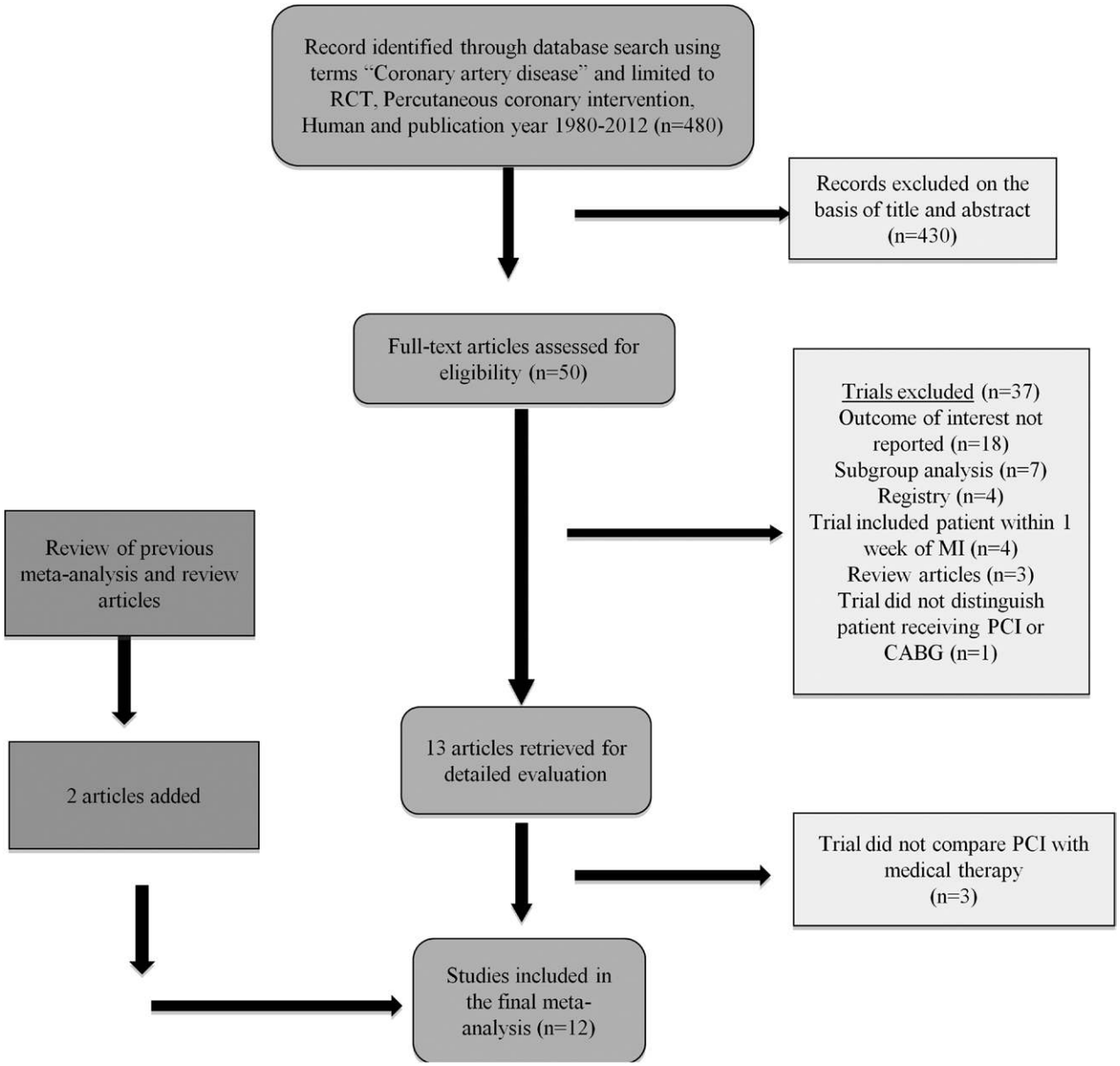

Figure 1. Study selection. CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; and RCT, randomized clinical trial.

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Table 1. Baseline Characteristics of Included Trials

Trial Name	No. of Patients	Age, y	Follow-up, y	Men, %	DM, %	Hypertension, %	Prior MI, %	Mean LDL,mg/dL	% Stenting in PCI Group
ACME-1[25,32]	212	62	3	100	18	52.5	30.5	106	0
ACME-2[23]	101	60	5	100	18	NR	45	NR	0
ALKK[34]	300	58	4.7	86	16	39	100	NR	17
AVERT[33]	341	58	1.5	84	16	45	42	144	30
BARI 2D[24]	1605	62	5	68	100	82	31	95	91
DEFER[20]	181	61	5	64	12	35	25	NR	46
COURAGE[21]	2287	62	4.6	85	34	66	38	101	88
JSAP[31]	384	64	3.3	75	40	63	14	120	76
MASS I[29,30]	144	56	5	81	17	36	0	151	0
MASS II[27,28]	408	60	5	85	14	28	22	148	72
RITA-2[19,26]	518	58	7	82	9	NR	47	NR	8
SWISSI II[22]	201	55	10.2	88	11	45	100	NR	0

ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DEFER, FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses; DM, diabetes mellitus; JSAP, Japanese Stable Angina Pectoris; LDL, low-density lipoprotein; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; RITA, Randomized Intervention Treatment of Angina; and SWISSI II, Swiss Interventional Study on Silent Ischemia Type II.

Procedural MI

PCI compared with OMT alone (event rate, 4.60 versus 1.01 per 1000 patient-years) was associated with a 317% increase in the IRR of procedural MI on the basis of a random-effects Poisson regression model (IRR=4.17; 95% CI, 2.53–6.88), and the results were similar when a summary-based random-effects

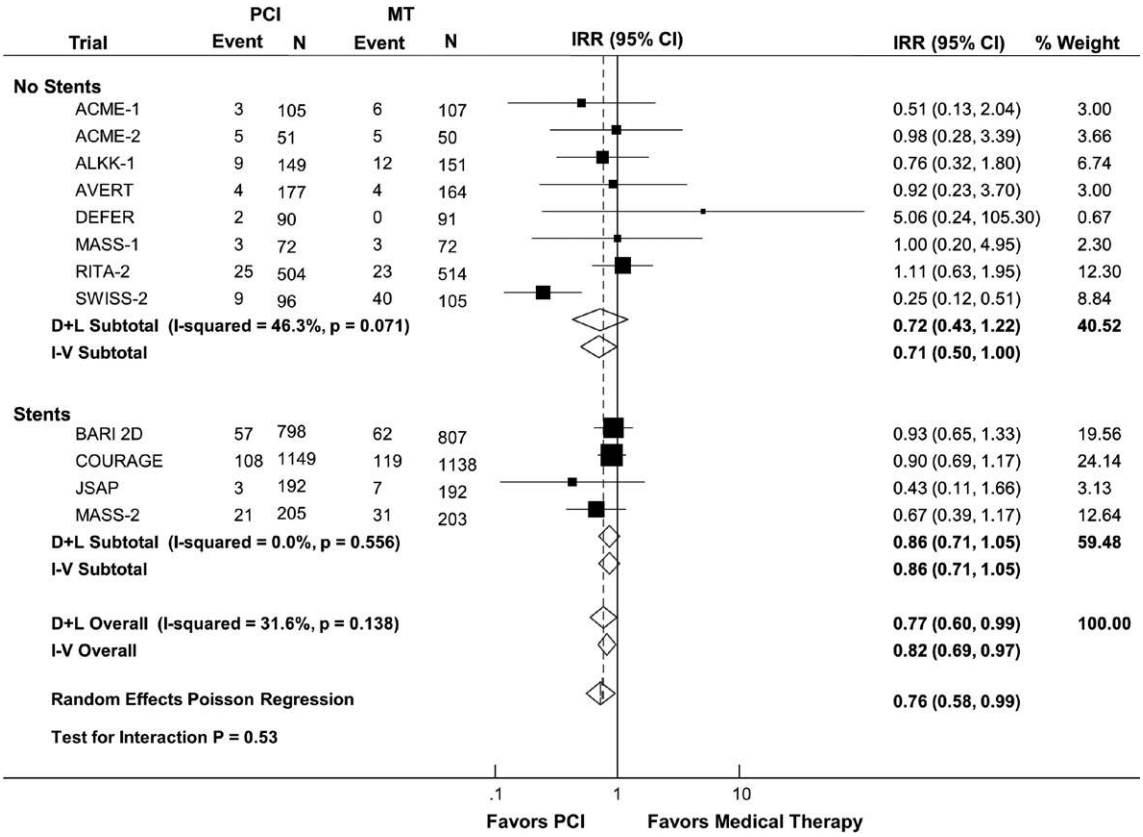

Figure 2. Percutaneous coronary intervention (PCI) vs optimal medical therapy (MT) for the outcome of spontaneous nonprocedural myocardial infarction. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin Versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; D+L, DerSimonian and Laird; IRR, incident rate ratio; I-V, inverse variance; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; and SWISS-2, Swiss Interventional Study on Silent Ischemia Type II (SWISSI II).

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model was used (IRR=3.22; 95% CI, 2.01–5.16) (Figure 3). There was no heterogeneity in the analysis (I^2=0%) with no evidence of publication bias (Egger's *P*=0.49; Begg's *P*=0.26) (Figure II in the online-only Data Supplement). The results were similar when no-stent and stent trials were analyzed separately ($P_{interaction}$=0.56).

All MI

For the outcome of all MI, there was no difference between PCI and OMT (event rate, 18.28 versus 18.31 per 1000 patient-years) (IRR=0.96; 95% CI, 0.74–1.21), with similar results when a summary-based random-effects model was used (IRR=0.94; 95% CI, 0.71–1.25) (Figure 4). There was moderate heterogeneity in the analysis (I^2=50%) with no evidence of publication bias (Egger's *P*=0.57; Begg's *P*=0.63) (Figure III in the online-only Data Supplement). The results were similar when no-stent and stent trials were analyzed separately ($P_{interaction}$=0.99).

Mortality

PCI compared with OMT alone was associated with a nonsignificantly different risk of all-cause mortality (event rate, 16.20 versus 18.47 per 1000 patient-years) (IRR=0.88; 95% CI, 0.75–1.03) (Figure 5) and cardiovascular mortality (event rate, 6.47 versus 8.01 per 1000 patient-years) (IRR=0.70; 95% CI, 0.44–1.09) (Figure 6). For cardiovascular mortality, the test for interaction was significant ($P_{interaction}$=0.03) such that PCI was associated with a reduction in cardiovascular mortality in the no-stent trials but not in the stent trials (Figure 6). The point estimate for PCI versus OMT for these outcomes paralleled that for spontaneous nonprocedural MI (but not procedural or all MI).

Sensitivity Analysis

Sensitivity analyses performed after trials without ischemia (AVERT and DEFER) were excluded showed results similar to those of the main analysis. Specifically, for spontaneous nonprocedural MI, the IRR was 0.79 (95% CI, 0.67–0.92), and that for all MI was 0.89 (95% CI, 0.68–1.17).

Meta-Regression Analysis

Meta-regression analysis for the outcome of all-cause death favored PCI for trials with lower usage of stents (*P*=0.23), higher achieved low-density lipoprotein levels in the OMT arm (*P*=0.49), and lower crossovers in the OMT arm (*P*=0.52), although none were statistically significant (Figure 7). Similarly, there was no significant relationship between

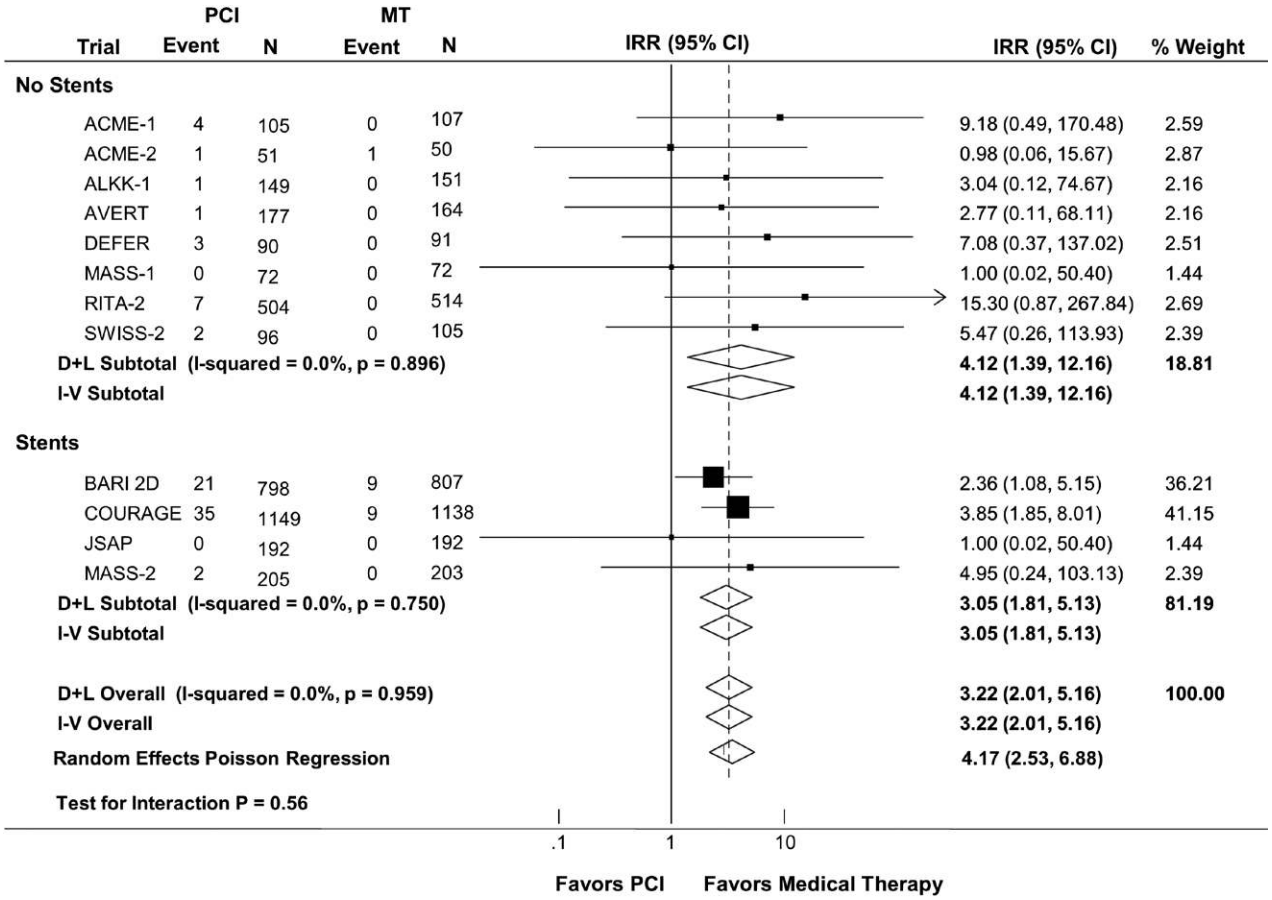

Figure 3. Percutaneous coronary intervention (PCI) vs optimal medical therapy (MT) for the outcome of procedural myocardial infarction. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin Versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; D+L, DerSimonian and Laird; IRR, incident rate ratio; I-V, Inverse variance; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; and SWISS-2, Swiss Interventional Study on Silent Ischemia Type II (SWISSI II).

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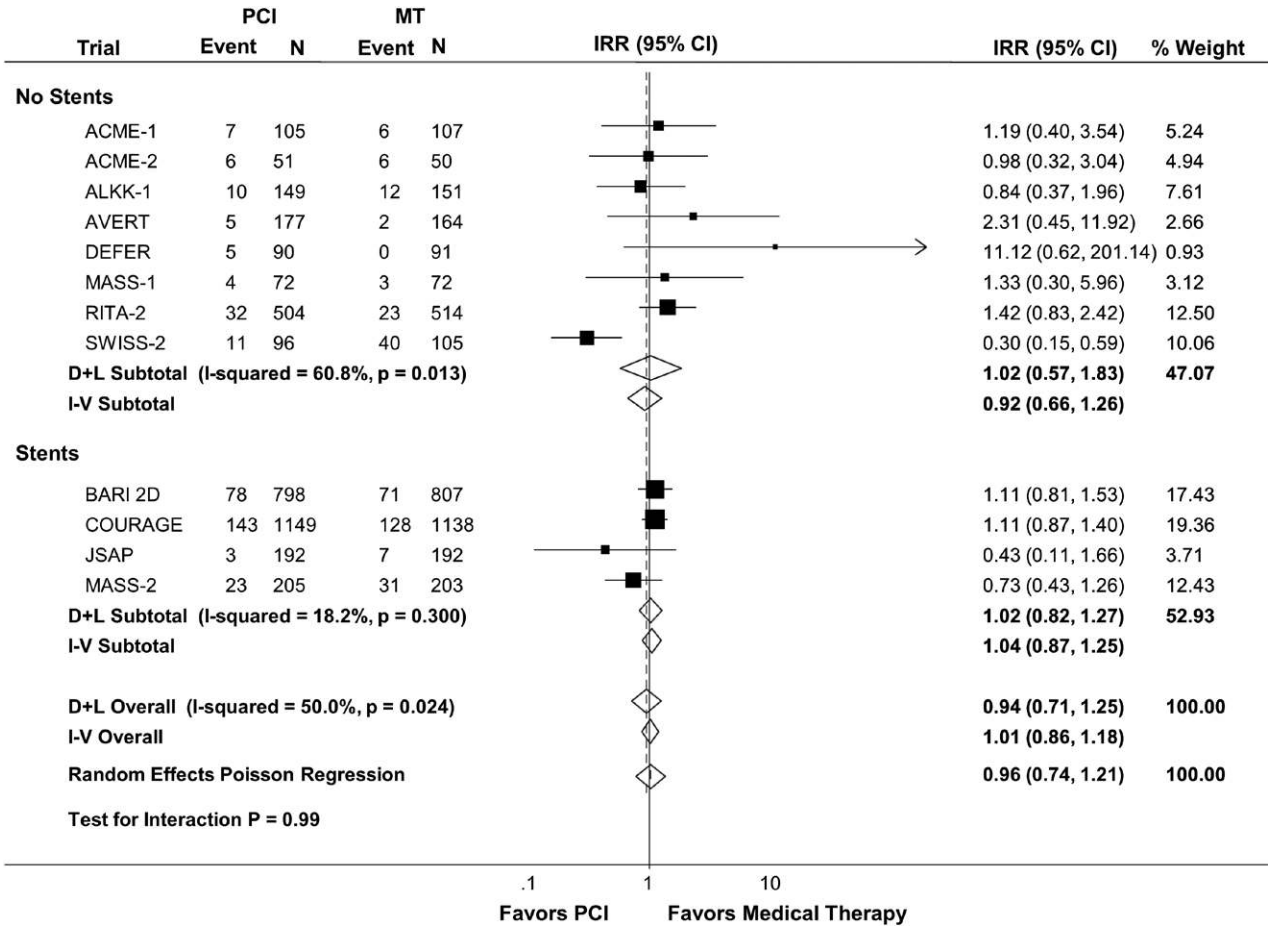

Figure 4. Percutaneous coronary intervention (PCI) vs optimal medical therapy (MT) for the outcome of all myocardial infarction. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin Versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; D+L, DerSimonian and Laird; IRR, incident rate ratio; JSAP, Japanese Stable Angina Pectoris; I-V, Inverse variance; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; and SWISS-2, Swiss Interventional Study on Silent Ischemia Type II (SWISSI II).

spontaneous MI and percentage of stents used, low-density lipoprotein levels, or crossovers in the OMT arm (Figures IV through VI in the online-only Data Supplement).

Discussion

The results of the present analyses of ≈37 500 patient-years of follow-up showed a statistically significant 24% relative reduction (absolute reduction of 3.62 per 1000 patient-years) in the risk of spontaneous nonprocedural MI at the risk of a 317% relative increase (absolute increase of 3.59 per 1000 patient-years) in the risk of procedural MI with PCI compared with OMT alone, with no difference in the risk of all MI. The point estimate for PCI versus OMT for the outcome of all-cause mortality and cardiovascular mortality paralleled that of spontaneous nonprocedural MI (but not procedural or all MI), suggesting that spontaneous nonprocedural MI may be prognostically more important than procedural or all MI.

Prognostic Value of Procedural MI

The prognostic value of procedural MI has been a matter of great controversy, with renewed interest of late. This is even more important because procedural MI is frequently included in the component primary end point definition of clinical trials of PCI. The issue is relatively less of a problem when the 2 arms of the trial have similar frequencies of a procedural MI, such as comparisons of 2 stents. However, in trials in which procedural MI preferentially occurs with higher frequency in one arm, such as PCI versus OMT trials, the definition and prognostic significance of these biomarker elevations assume significance because the trial interpretation will change on the basis of the frequency of these events.

The new universal definition of procedural MI (type 4a) includes increases >5 times the 99th percentile of the upper reference limit of troponin (I or T) after PCI.[35] However, the universal definition committee recognized that there was no solid scientific basis for recommending this threshold,[35] and it is therefore controversial. The issue is exemplified by recent data suggesting different frequencies of procedural MI depending on whether creatine kinase MB (CK-MB) or troponin is used as the biomarker. In the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry of patients undergoing elective PCI, the rate of procedural MI was 7.2% when CK-MB was used but was almost 3 times higher when

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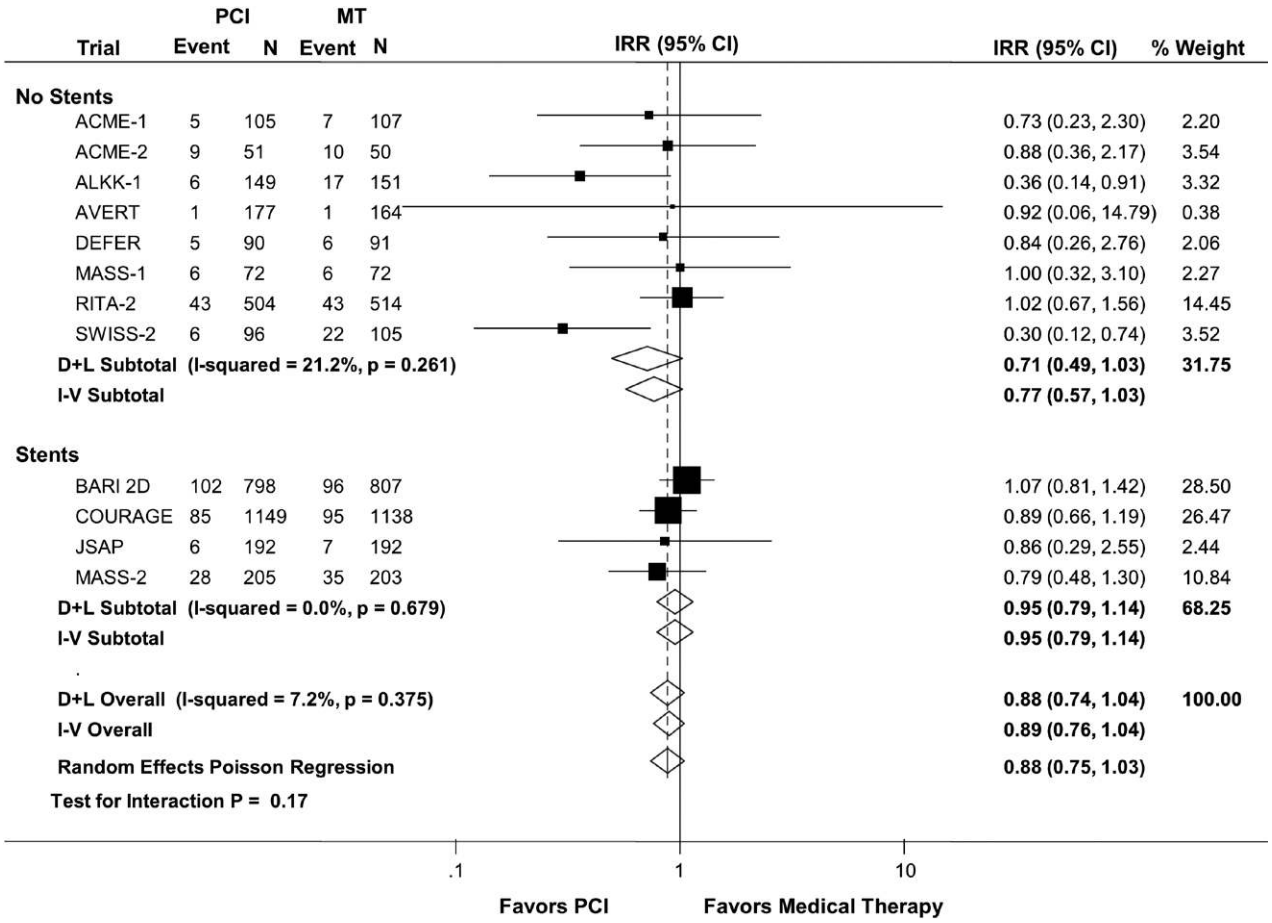

Figure 5. Percutaneous coronary intervention (PCI) vs optimal medical therapy (MT) for the outcome of all-cause mortality. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin Versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; D+L, DerSimonian and Laird; IRR, incident rate ratio; JSAP, Japanese Stable Angina Pectoris; I-V, Inverse variance; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; and SWISS-2, Swiss Interventional Study on Silent Ischemia Type II (SWISSI II).

troponin was used (24.3%).[9] Other studies have similarly observed procedural MI rates as high as 48% when troponins were used[36] or when other definitions were used.[6]

In addition to the frequency of occurrence of these events, the prognostic value of procedural MI itself has been questioned. Although a few studies have shown a positive association of biomarker elevation with mortality,[8,9,36–40] others have shown a higher biomarker threshold (especially with the universal definition recommended for troponin) for such prognostic significance.[9,36] In the EVENT registry analysis, troponin levels >20 times the upper reference limit were equal to the prognostic importance of a 3-fold elevation in CK-MB.[9] Others have shown no association of biomarker (especially troponin) elevation with prognosis.[4,5] In an analysis of 3687 patients from the Prospective, Randomized Trial Comparing an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease (SPIRIT IV), there was no association between procedural MI and mortality up to 2 years, even at high levels of CK-MB or troponin elevation (>10 times the upper reference limit).[6] In a collaborative analysis from the Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC) II trial, Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial, and Randomised Intervention Trial of Unstable Angina (RITA)-3 trial, spontaneous MI and not procedural MI was a significant predictor of cardiovascular death at 5 years.[3] Similarly, in an analysis from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, spontaneous MI and not procedural MI was a powerful predictor of mortality at 1 year.[1] Finally, in the largest study thus far, with data from >23 604 patients from 11 studies, spontaneous MI and not procedural MI was a significant predictor of intermediate- and long-term mortality after multivariable adjustments.[2] In our analyses, the point estimate for hard outcomes of cardiovascular mortality and all-cause mortality paralleled that for spontaneous nonprocedural MI but not procedural or all MI, suggesting that spontaneous nonprocedural MI may be prognostically more important. However, this is an indirect inference.

PCI Versus OMT Trials

It has become increasingly clear that the prognostic impact of procedural MI is not the same as that of spontaneous MI,

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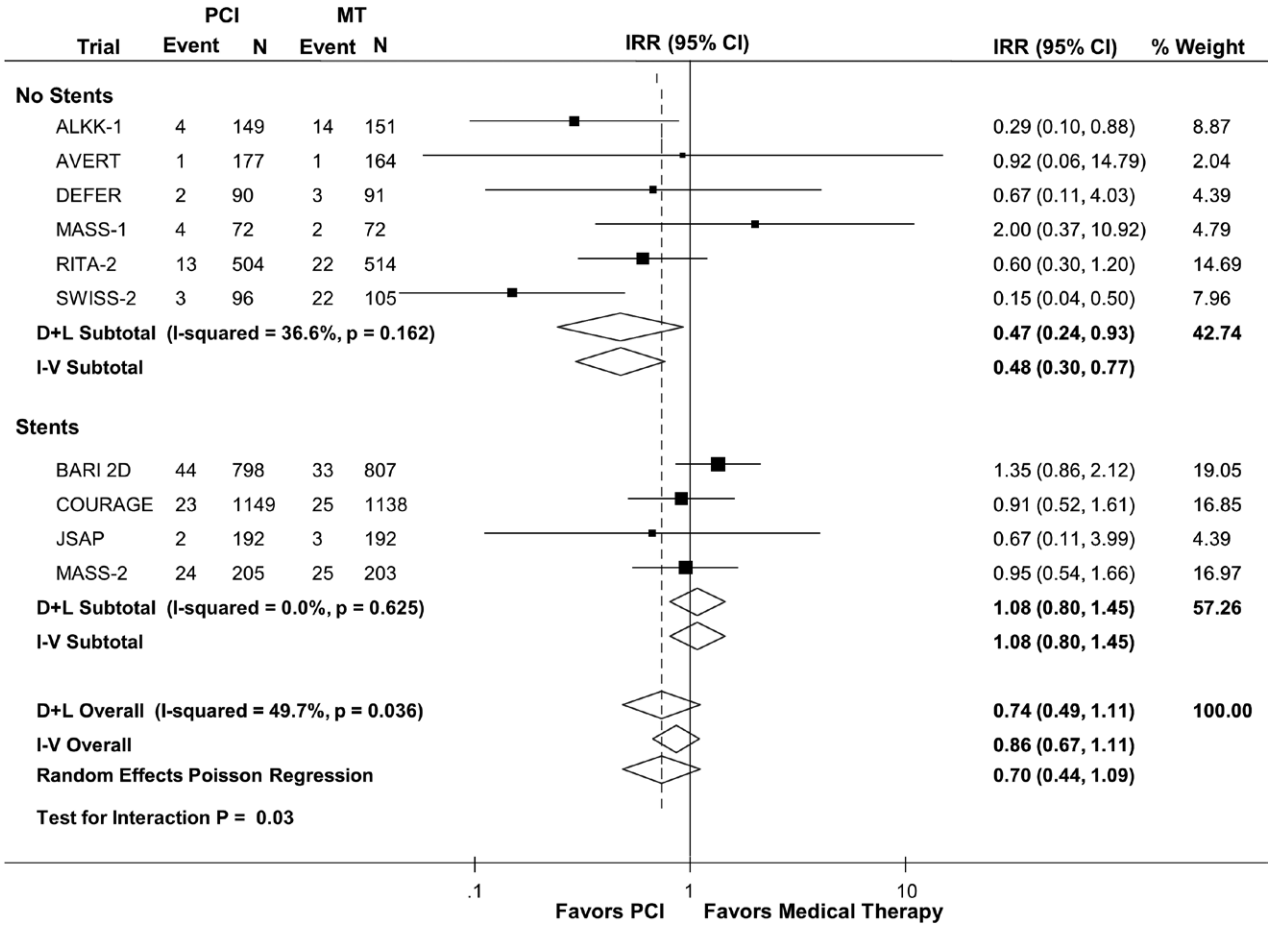

Figure 6. Percutaneous coronary intervention (PCI) vs optimal medical therapy (MT) for the outcome of cardiovascular mortality. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin Versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; D+L, DerSimonian and Laird; IRR, incident rate ratio; I-V, inverse variance; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; and SWISS-2, Swiss Interventional Study on Silent Ischemia Type II (SWISSI II).

and combining both in the definition of any MI, especially in trials of PCI versus OMT, is problematic. As shown by the results of this analysis, PCI was associated with a significant decrease in the IRR of spontaneous MI, a significant increase in the risk of procedural MI, and no difference for the risk of any MI compared with OMT. The results are somewhat consistent with an analysis from the New York State Angioplasty Registry, in which PCI was associated with a significant decrease in death and death or MI compared with routine medical therapy alone.[41] Although selection bias, baseline confounders, and less than optimal medical therapy could have driven the results of the New York State Angioplasty Registry, the MIs assessed were largely spontaneous MIs because routine biomarker collection and reporting after PCI is not mandatory in New York State. It is therefore worthwhile to examine real-world clinical practice as it relates to procedural MI. In an analysis of 213 395 patients who underwent elective PCI at 463 hospitals with no reported evidence of myocardial necrosis before the PCI procedure, only 7% of patients had postprocedure CK-MB levels measured across all hospitals, suggesting that this is practiced rarely in routine clinical care.[42] If the results of the PCI versus OMT trials are true (with no difference in MI) and are to be seen in routine clinical practice, postprocedure marker measurement needs to be implemented universally. This only applies if procedural MI is determined to be prognostically important in future studies. Until that time, equating the prognostic significance of procedural MI with that of spontaneous MI in clinical trials is problematic and should not be done. Further studies are urgently needed to evaluate the prognostic importance of these different types of MI.

The recently published third universal definition of MI states that "MI associated with PCI is arbitrarily defined by elevation of cTn values >5 × 99th percentile upper reference limit in patients with normal baseline values or a rise of cTn values >20% if the baseline values are elevated and are stable or falling."[43] In addition to biomarker criteria, the revised universal definition also requires the presence of one other additional criterion (from among symptoms, ECG changes, angiographic complications, or imaging evidence of new loss of viable myocardium). This definition is an attempt to increase specificity and move away from biomarker-only criteria and appears to be a step in the right

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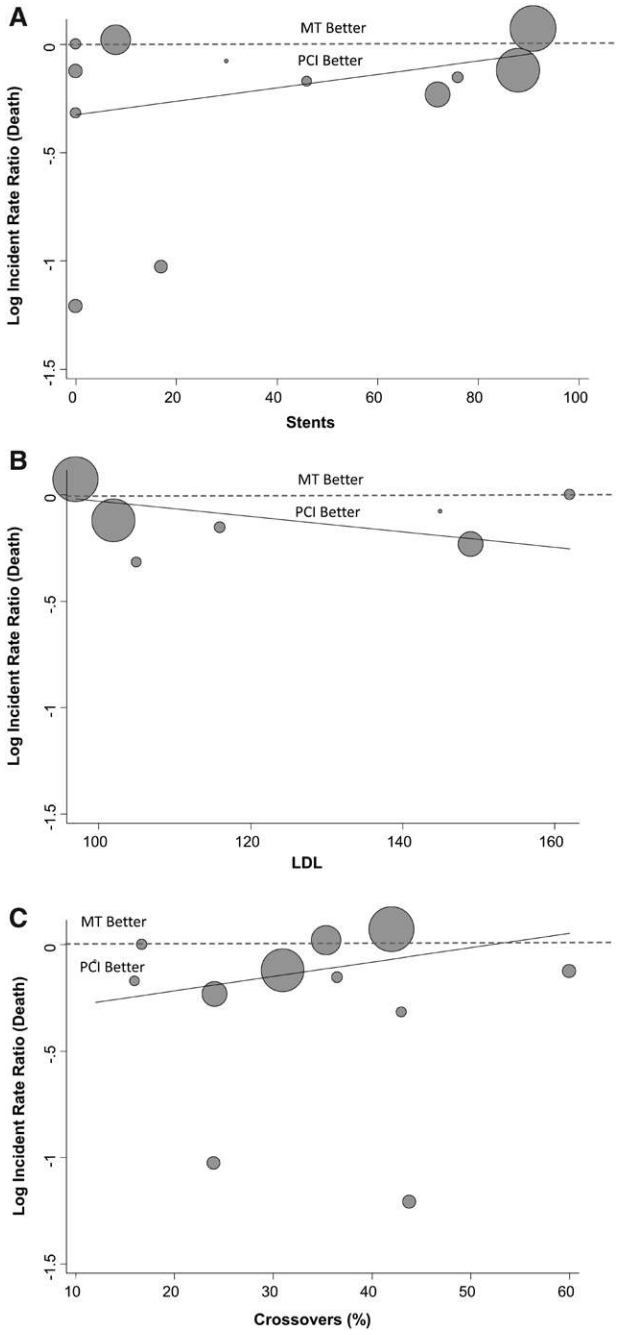

Figure 7. A, Influence of percentage of stents used in the percutaneous coronary intervention (PCI) group on the incident rate ratio for the outcome of death. **B**, Influence of achieved low-density lipoprotein (LDL) cholesterol levels in the optimal medical therapy (MT) group on the incident rate ratio for the outcome of death. **C**, Influence of crossovers in the optimal MT group on the incident rate ratio for the outcome of death.

direction. However, as acknowledged by the committee, the definition is arbitrary, and more data are needed to evaluate the prognostic significance of this revised procedural MI definition.

Finally, the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial will enroll 8000 patients and will have >90% power to detect a 15% to 17% reduction in cardiovascular death or MI in patients randomized to an invasive strategy of cardiac catheterization with revascularization compared with a conservative strategy of OMT alone and will provide more evidence in regard to the optimal management of patients with stable ischemic heart disease.[44] Given the large sample size of the trial, it will offer opportunities to test the long-term prognostic significance of various definitions of procedural MI.

Study Limitations

As in other meta-analyses, given the lack of data in each trial, we did not adjust our analyses for compliance with assigned treatment, stent type used, or dosage of the medications used. Although detailed sensitivity analyses on many variables were undertaken, given the heterogeneity in the study protocols, clinically relevant differences could have been missed and are best assessed in a meta-analysis of individual patient data. Although there was no major statistical heterogeneity in the analyses, there was clinical heterogeneity in the included studies, including trial design, patient population studied, aggressiveness of medical therapy, and PCI techniques, including usage of stents. The subgroup analyses might suffer from multiple testing. The results of the sensitivity analyses are best described as secondary and hypothesis generating only. Only 4 trials used stents, and the majority of stents implanted were bare metal stents. In addition, in the minority of patients in whom DES were used, newer-generation DES such as everolimus-eluting stents, which have been shown to have a lower stent thrombosis rate than even a bare metal stent,[45] were not used. Whereas the use of stents has been predominantly shown to reduce the incidence of restenosis over balloon angioplasty alone, restenosis is in itself not a benign phenomenon, with one third to one half of patients with restenosis presenting with acute coronary syndrome.[46,47] We have recently shown that DES and especially newer-generation DES, such as everolimus-eluting stents, reduce the risk of MI compared with bare metal stents alone, attesting to the importance of reducing the risk of restenosis.[48] Of note, data from the Fractional Flow Reserve Guided PCI Versus Medical Therapy in Stable CAD (FAME) II trial[49] could not be included because the rates of spontaneous versus procedural MIs were not available, even after the authors were contacted.

Conclusions

In patients with stable ischemic heart disease, PCI compared with OMT alone was associated with significant reduction in the risk of spontaneous non–procedure-related MI at the risk of procedural MI with no difference in all MI. The present report shows that the point estimate for mortality parallels the prevention of spontaneous MI but not procedural MI, suggesting that spontaneous non–procedure-related MI is prognostically more important, consistent with recently published reports. Further trials are needed to determine whether these associations are causal.

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Table 2. Selected Characteristics of Included Trials

Trial	Inclusion Criteria	Exclusion Criteria	Definition of MI	Quality Assessment*	Description of Medical Therapy
ACME-1[25,32]	70–99% stenosis in proximal two thirds of 1 major coronary artery, stress test with ≥1 mm ST depression in at least 1 lead or filling defect on thallium scan, or MI in past 3 mo	Not reported	New Q wave on ECG or increase in CK level above normal with typical clinical signs	+±±+++	325 mg aspirin, nitrates, β-blockers, CCBs
ACME-2[23]	History of angina, MI within 3 mo, or ≥3 mm horizontal ST depression on exercise testing; ≥70% stenosis in proximal two thirds of 1 or 2 coronary arteries (data for 1-vessel CAD previously presented as ACME-1)	Medically refractory unstable angina, prior PCI, primary cardiac diagnosis other than CAD, ≥50% left main stenosis, 3-vessel CAD, LVEF ≤30%	New Q wave (≥0.04-s duration or ≥25% total QRS voltage) in any anterior or lateral lead or in ≥2 contiguous inferior leads on follow-up ECG or hospital admission for chest pain accompanied by serum biomarkerchanges meeting local hospital criteria for MI	+±++++	Aspirin plus individualized therapy of nitrates, β-blockers, CCBs
ALKK[34]†	Post-STEMI 8–42 days with feasible PTCA or recanalization of culprit artery, CCS class I or II angina	CCS class III or IV angina, >70% stenosis in another coronary artery, CABG as infarct vessel, need for CABG (left main stenosis, LV aneurysm, significant valve disease), noncardiac disease reducing life expectancy	Typical chest pain of ≥30 min, ST elevations in ≥1 continuous ECG leads, and development of elevations of the CK or CK-MB fraction or ≥2 new Q waves on 12-lead ECG	++±+++	100 mg aspirin, β-blockers, and additional medications per physician discretion
AVERT[33]†	≥50% stenosis of at least 1 coronary artery for which PCI was recommended, asymptomatic or with CCS class I or II angina, completion of at least 4 min of stress test without ischemia, LDL ≥115 mg/dL, and triglycerides <500 mg/dL	Left main disease, 3-vessel CAD, unstable angina, MI in prior 2 wk, LVEF <40%	Not reported	+±−+++	80 mg atorvastatin
BARI 2D[24]†	≥50% stenosis of major coronary artery with positive stress test or ≥70% stenosis of major coronary artery with classic angina and type 2 diabetes mellitus	Need for immediate revascularization, left main disease, creatinine >2 mg/dL, HbA_{1c} >13%, class III or IV heart failure, hepatic dysfunction, PCI or CABG in previous 12 mo	Spontaneous MI as doubling of cardiac biomarkers (CK-MB or troponin) and evidence of ischemiaon the basis of symptoms, ECG, or imaging; silent MI as a Q-wave change of 2 grades on routine ECG; procedure related as CK-MB elevation of 3 times and 10 times above normal for PCI and CABG, respectively	++++++	Aspirin, statins, β-blockers, and ACEi or ARB; insulin and/or oral hypoglycemic therapy
DEFER[20]	Angiography with >50% stenosis in native coronary artery and FFR ≥0.75, no evidence of reversible ischemia by noninvasive testing within the previous 2 mo	Total occlusion of the target artery, Q-wave infarction, unstable angina, or small target arteries	New pathological Q waves on ECG or increase of serum CK levels to >2 times normal value	+±++++	Statins, β-blockers, nitrates
COURAGE[21]	≥70% stenosis in at least 1 proximal artery, inducible ischemia on stress testing, or ST depression or T-wave inversion on resting ECG	CCS class IV angina, substantial ST depression or hypotension during Bruce protocol stage 1 stress testing, refractory heart failure or cardiogenic shock, LVEF <30%, revascularization in prior 6 mo, coronary anatomy not suitable for PCI	Clinical presentation consistent with an ACS and either new abnormal Q waves in ≥2 ECG leads or positive results in cardiac biomarkers; silent as abnormal Q waves, confirmed by a corelaboratory	++++++	81–325 mg aspirin and/or 75 mg clopidogrel; long-acting metoprolol and/or amlodipine and/or nitrates; lisinopril or losartan; simvastatin alone or with ezetimibe; extended-release niacin and/or fibrates if needed

(*Continued*)

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Table 2. (*Continued*)

Trial	Inclusion Criteria	Exclusion Criteria	Definition of MI	Quality Assessment*	Description of Medical Therapy
JSAP[31]†	≥75% (or ≥60% on quantitative coronary angiography) 1- or 2-vessel CAD, inducible ischemia on stress testing or ST depression or T-wave inversion on resting ECG	3-vessel CAD, left main or ostial LAD disease, total occlusion, ACS, LVEF <50%, tendency to bleed, disseminated intravascular coagulation, severe pneumonia, creatinine >1.5 mg/dL, graft stenosis, low-risk CAD where PCI or medical therapy had already been prescribed	New abnormal Q waves in ≥2 ECG leads during follow-up, or convincing clinical history associated with ECG changes compatible with non–Q-wave infarction, and serum level of ≥2 cardiac biomarkers greater than twice normal	++++++	Entirely physician dependent (majority received aspirin or other antiplatelet, β-blockers, nitrates, statins, ACEi/ARB)
MASS I[29,30]	≥80% LAD stenosis before takeoff of first diagonal branch, single-vessel CAD	Total occlusion, lesion length >12 mm, involvement of the ostium, heavy calcification, severe tortuosity, left main disease, unstable angina, prior MI, significant valvular disease, cardiomyopathy, LV dysfunction, prior PCI or CABG	Significant new Q waves in ≥2 ECG leads or symptoms compatible with MI associated with elevation of the CK-MB fraction >3 times upper limit of normal	+±±+++	Aspirin, nitrates, β-blockers
MASS II[27,28]	≥70% proximal multivessel stenosis and documented ischemia by stress testing or CCS class II or III	Unstable angina, acute MI requiring emergent revascularization, ventricular aneurysm requiring surgical repair, LVEF <40%, prior PCI or CABG, single-vessel CAD, congenital heart disease, valvular heart disease, cardiomyopathy, left main stenosis ≥50%, unable to comply with protocol or follow-up, suspected or known pregnancy	Significant new Q waves in ≥2 ECG leads or symptoms compatible with MI associated with elevation of the CK-MB fraction >3 times the upper limit of normal	+±±+++	Aspirin, nitrates, β-blockers, CCBs, ACEi, statins
RITA-2[19,26]	Angiography with ≥50% (2 views) or ≥70% (1 view) stenosis in at least 1 major artery amenable to PTCA, recent unstable angina at least 7 d before randomization	Revascularization necessary for symptom relief or prognostic benefit, prior revascularization, significant left main disease, ACS in the previous 7 d, hemodynamically significant valve disease, or life-threatening noncardiac disease	New pathological Q waves (>30 ms in duration) on anECG within 7 d of any myocardial revascularization procedure (procedure-related infarction) or during subsequent follow-up or typical clinical history associated with ECG changes compatible with non–Q-wave infarction and serum levels of ≥2 cardiac biomarkers above twice normal	+±++++	Aspirin, β-blockers, CCBs, long-acting nitrates at maximally tolerated doses, lipid-lowering drugs only as needed
SWISSI II[22]†	First STEMI or non-STEMI within 3 preceding mo, no malignancy, 1- to 2-vessel CAD on angiography and silent ischemia on maximal exercise stress testing with imaging	3-vessel CAD, coronary lesions not technically amenable to PCI	Typical chest pain, ST-segment elevation on ECG, and/or a typical increase and decrease of cardiac biomarkers according to definitions of the European Society of Cardiology; silent MI as presence of new Q waves on resting ECG documented by new distinct wall motion abnormalities on restingechocardiogram with a decrease in LVEF of ≥5% and/or a reduction in LVEF of >10% vs a previous echocardiography	++++++	100 mg aspirin, statin, 5–10 mg bisoprolol, 5–10 mg amlodipine, 4–12 mg BID molsidomine; ACEi inhibitor if hypertensive

ACEi indicates angiotensin-converting enzyme inhibitor; ACME, Angioplasty Compared to Medicine; ACS, acute coronary syndrome; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; ARB, angiotensin receptor blocker; AVERT, Atorvastatin versus Revascularization Treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society; CK, creatinine kinase; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DEFER, FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses; DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; JSAP, Japanese Stable Angina Pectoris; LDL, low-density lipoprotein; LV, left ventricular; LVEF, left ventricular ejection fraction; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RITA, Randomized Intervention Treatment of Angina; STEMI, ST-segment elevation MI; and SWISSI II, Swiss Interventional Study on Silent Ischemia Type II.

*Represents risk of bias based on sequence generation of allocation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. + represents low bias risk; –, high bias risk; and ±, unclear bias risk.

†Additional data from author correspondence.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Contemporary studies have shown that spontaneous myocardial infarction (MI) but not procedural MI is related to subsequent mortality. In trials in which procedural MI preferentially occurs with higher frequency in one arm, such as percutaneous coronary intervention versus optimal medical therapy trials, the definition and prognostic significance of these biomarker elevations assume significance because the trial interpretation will change on the basis of the frequency of these events. Procedural MI, which occurs at a frequency as high as 50% on the basis of the biomarker tested and the definition used, has the potential to completely change the results of clinical trials. In the present study of patients with stable ischemic heart disease, percutaneous coronary intervention compared with optimal medical therapy alone was associated with significant reduction in the risk of spontaneous non–procedure-related MI at the risk of procedural MI with no difference in all MI, thus suggesting that the interpretation of these trials varies depending on the MI definition used. The present report shows that the point estimate for mortality parallels the prevention of spontaneous MI but not procedural MI, suggesting that spontaneous non–procedure-related MI is prognostically more important, consistent with recently published reports. Further trials are needed to determine whether these associations are causal. If the results of the percutaneous coronary intervention versus optimal medical therapy trials are true (with no difference in MI) and are to be seen in routine clinical practice, postprocedure marker measurement (rarely drawn routinely in the United States) needs to be implemented universally. This only applies if procedural MI is determined to be prognostically important in future studies.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Details of MeSH Search Terms

Database	MeSH terms
MEDLINE via Pubmed	((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("Angina Pectoris"[MeSH Terms] OR "Angina"[TW] OR "Stable angina"[TW] OR "Myocardial ischemia"[TW] OR "Coronary disease"[MeSH Terms] OR "Atherosclerosis, Coronary"[TW] OR ("Non-acute"[all fields] AND "Coronary disease"[all fields]) OR ("Non acute"[all fields] AND "Coronary disease"[all fields]) OR "Arteriosclerosis, Coronary"[TW] OR "CAD"[TW] OR "CHD"[TW] OR "Coronary stenosis"[MeSH Terms] OR "Coronary stenoses"[TW]) AND ("Angioplasty, balloon, coronary"[MeSH] OR "Percutaneous transluminal coronary angioplasty"[TW] OR "Angioplasty, Balloon, Coronary"[MeSH Terms] OR "Cardiac catheterization"[TW] OR "Heart catheterization"[TW] OR "Drug-eluting stent"[TW] OR "Drug-eluting stents"[TW] OR "Drug eluting stent"[TW] OR "Bare metal stent"[TW] OR "Percutaneous coronary intervention"[TW] OR "PCI"[TW] OR "PTCA"[TW] OR "Angioplasty"[TW]) AND ("Conservative therapy"[TW] OR "Medical therapy"[TW] OR "Antihypertensive agents"[MeSH Terms] OR "Antihypertensive agent*"[TW] OR "Calcium channel blockers"[MeSH Terms] OR "Calcium channel blocker"[TW] OR "Calcium channel blockers"[TW] OR "Aspirin"[TW] OR "Nitroglycerin"[TW] OR "Nitric oxide donors"[MeSH Terms] OR "Nitric oxide donor"[TW] OR "Nitric oxide donors"[TW] OR "Anticholesteremic agents"[MeSH Terms] OR "Anticholesteremic"[TW] OR "Lipid regulating agents"[MeSH Terms] OR "Lipid regulating agents"[TW] OR "Lipid regulating agents"[MeSH Terms] OR "exercise therapy"[MeSH Terms] OR "Statin"[TW] OR "Statins"[TW])
EMBASE	'coronary stenosis':ab,ti OR 'coronary stenoses':ab,ti OR 'coronary artery atherosclerosis'/de OR 'stable angina pectoris'/de OR 'heart muscle ischemia'/de OR 'myocardial ischemia' OR 'coronary disease':ab,ti OR 'non-acute coronary disease':ab,ti OR 'non acute coronary disease':ab,ti OR 'cad':ab,ti OR 'chd':ab,ti AND ('transluminal coronary angioplasty'/exp OR 'heart catheterization'/exp OR 'drug eluting stent'/de OR 'bare metal stent'/de OR 'coronary stent'/de OR 'percutaneous coronary intervention'/exp OR 'percutaneous transluminal coronary angioplasty':ab,ti OR 'cardiac catheterization':ab,ti OR 'heart catheterization':ab,ti OR 'drug eluting stent':ab,ti OR 'drug eluting stents':ab,ti OR 'bare metal stent':ab,ti OR 'bare metal stents':ab,ti OR 'percutaneous coronary intervention':ab,ti OR 'pci':ab,ti OR 'ptca':ab,ti) AND ('antihypertensive agent'/de OR 'calcium channel blocking agent'/de OR 'aspirin':ab,ti OR 'nitric oxide donor':ab,ti OR 'antilipemic agent'/exp OR 'statins':ab,ti OR 'statin':ab,ti) NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp))
COCHRANE library	("Angina Pectoris"[MeSH Terms] OR "Angina"[TW] OR "Stable angina"[TW] OR "Myocardial ischemia"[TW] OR "Coronary disease"[MeSH Terms] OR "Atherosclerosis, Coronary"[TW] OR ("Non-acute"[all fields] AND "Coronary disease"[all fields]) OR ("Non acute"[all fields] AND "Coronary disease"[all fields]) OR "Arteriosclerosis, Coronary"[TW] OR "CAD"[TW] OR "CHD"[TW] OR "Coronary stenosis"[MeSH Terms] OR "Coronary stenoses"[TW]) AND ("Angioplasty, balloon, coronary"[MeSH] OR "Percutaneous transluminal coronary angioplasty"[TW] OR "Angioplasty, Balloon, Coronary"[MeSH Terms] OR "Cardiac catheterization"[TW]

	OR "Heart catheterization"[TW] OR "Drug-eluting stent"[TW] OR "Drug-eluting stents"[TW] OR "Drug eluting stent*"[TW] OR "Bare metal stent*"[TW] OR "Percutaneous coronary intervention"[TW] OR "PCI"[TW] OR "PTCA"[TW] OR "Angioplasty"[TW]) AND ("Conservative therapy"[TW] OR "Medical therapy"[TW] OR "Antihypertensive agents"[MeSH Terms] OR "Antihypertensive agent*"[TW] OR "Calcium channel blockers"[MeSH Terms] OR "Calcium channel blocker"[TW] OR "Calcium channel blockers"[TW] OR "Aspirin"[TW] OR "Nitroglycerin"[TW] OR "Nitric oxide donors"[MeSH Terms] OR "Nitric oxide donor"[TW] OR "Nitric oxide donors"[TW] OR "Anticholesteremic agents"[MeSH Terms] OR "Anticholesteremic"[TW] OR "Lipid regulating agents"[MeSH Terms] OR "Lipid regulating agents"[TW] OR "Lipid regulating agents"[MeSH Terms] OR "exercise therapy"[MeSH Terms] OR "Statin"[TW] OR "Statins"[TW])

Supplemental Figure Legends

Supplemental Figure 1. Funnel plot for the outcome of spontaneous non-procedural MI

Supplemental Figure 2. Funnel plot for the outcome of procedural MI

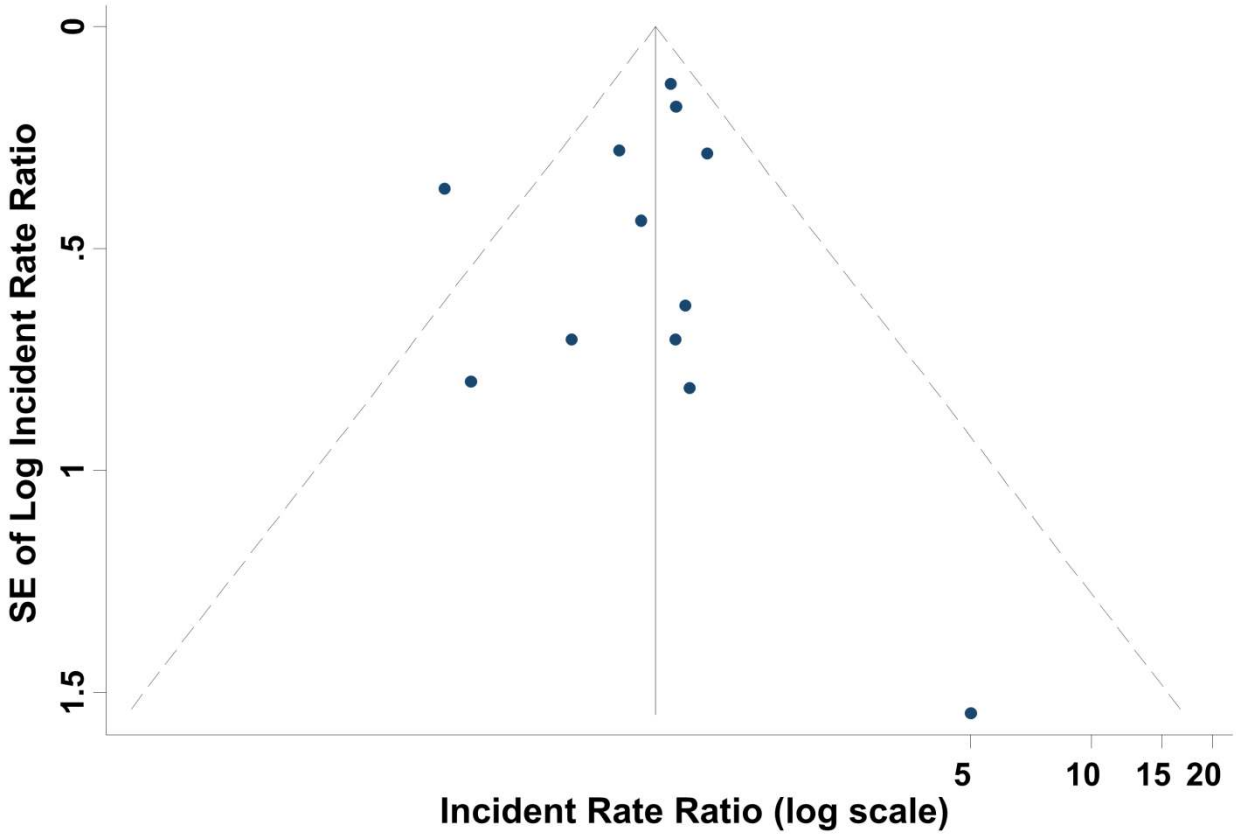
Supplemental Figure 3. Funnel plot for the outcome of all non-fatal MI

Supplemental Figure 4. Influence of percentage stents used in the PCI group on the incident rate ratio for the outcome of spontaneous MI.

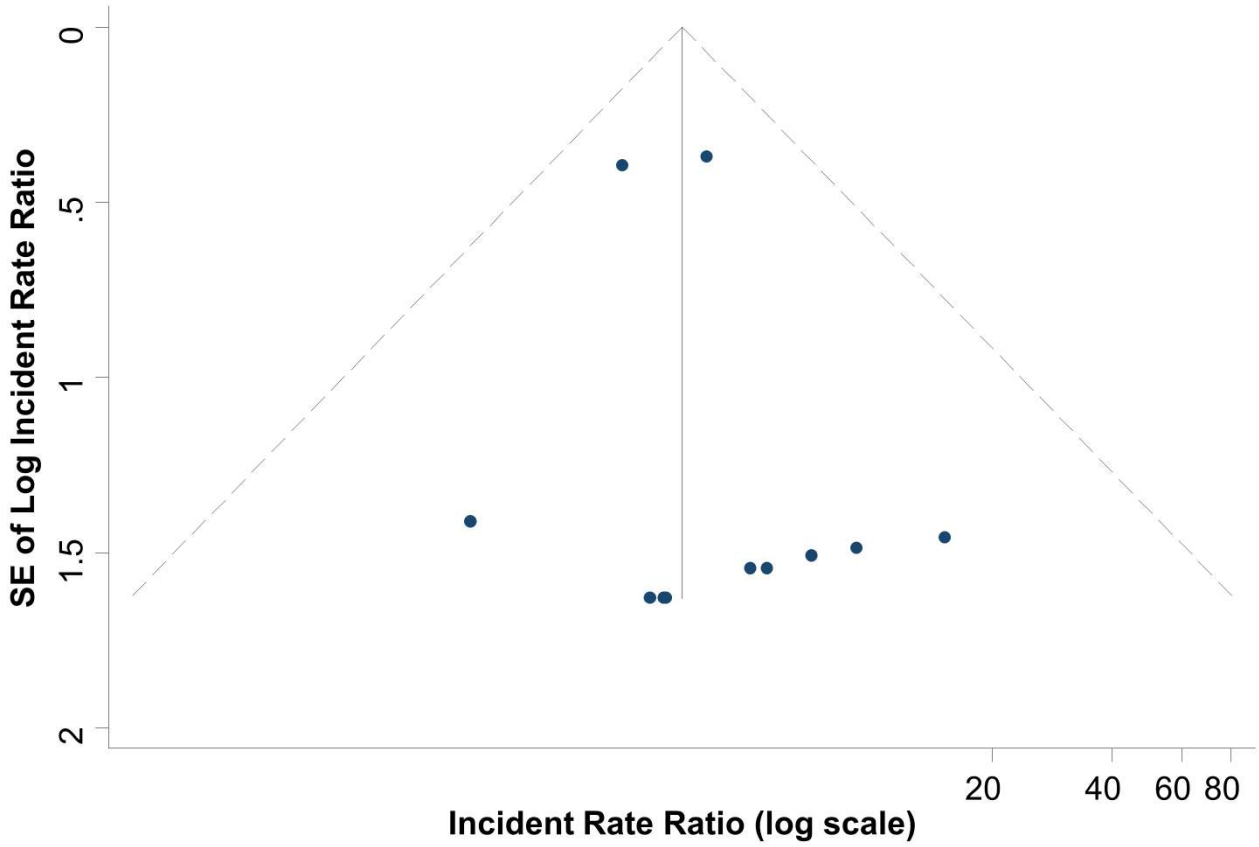
Supplemental Figure 5. Influence of achieved LDL cholesterol levels in the OMT group on the incident rate ratio for the outcome of spontaneous MI.

Supplemental Figure 6. Influence of crossovers in the OMT group on the incident rate ratio for the outcome of spontaneous MI.

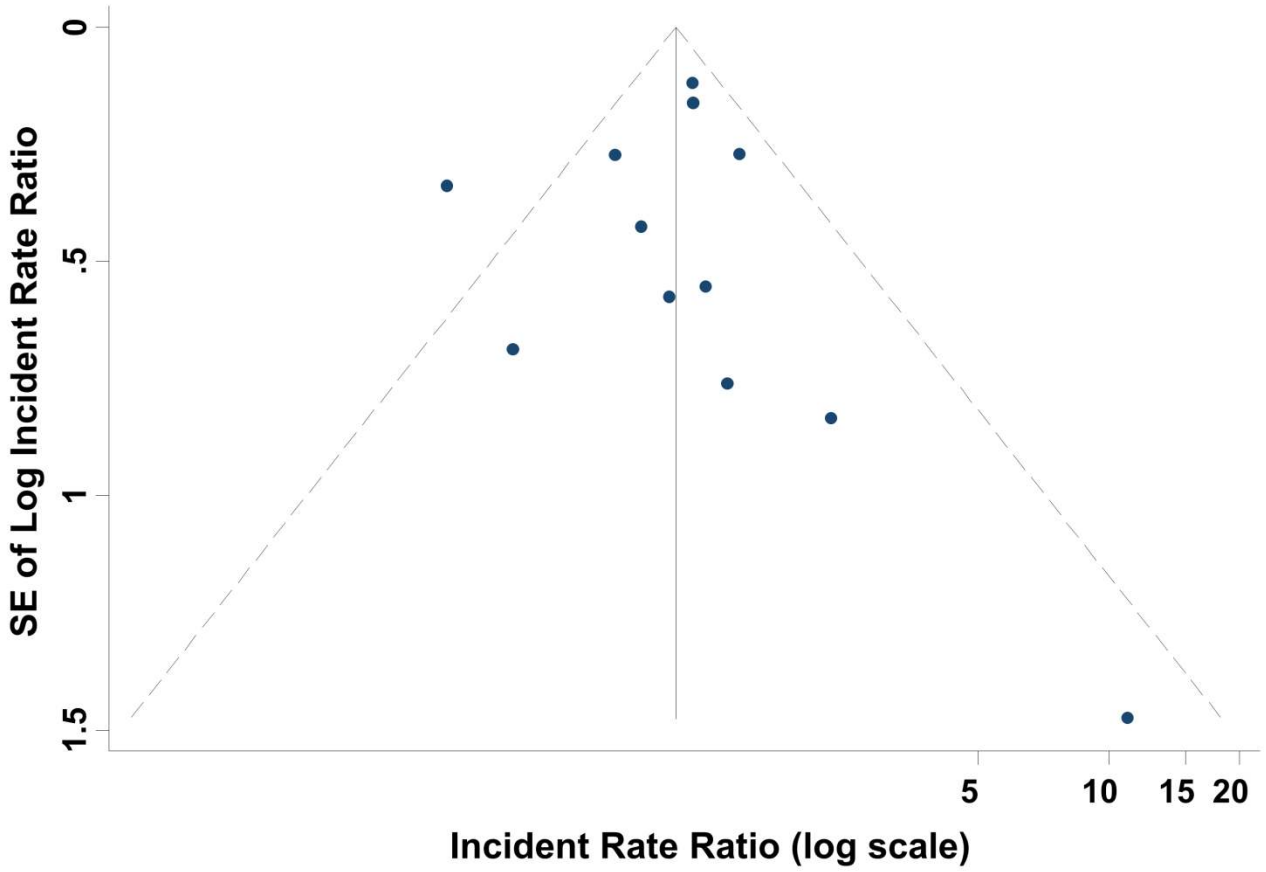
Supplemental Figure 1. Funnel plot for the outcome of spontaneous non-procedural MI



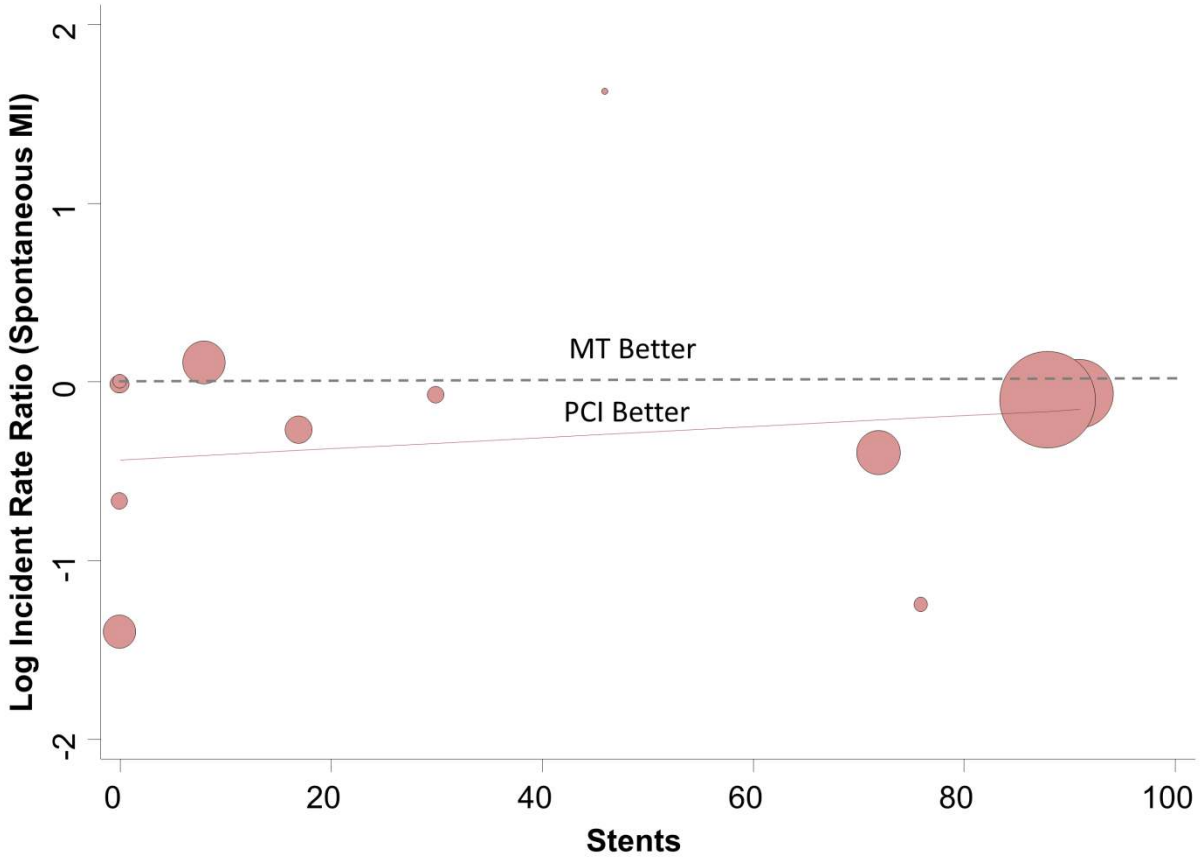
Supplemental Figure 2. Funnel plot for the outcome of procedural MI



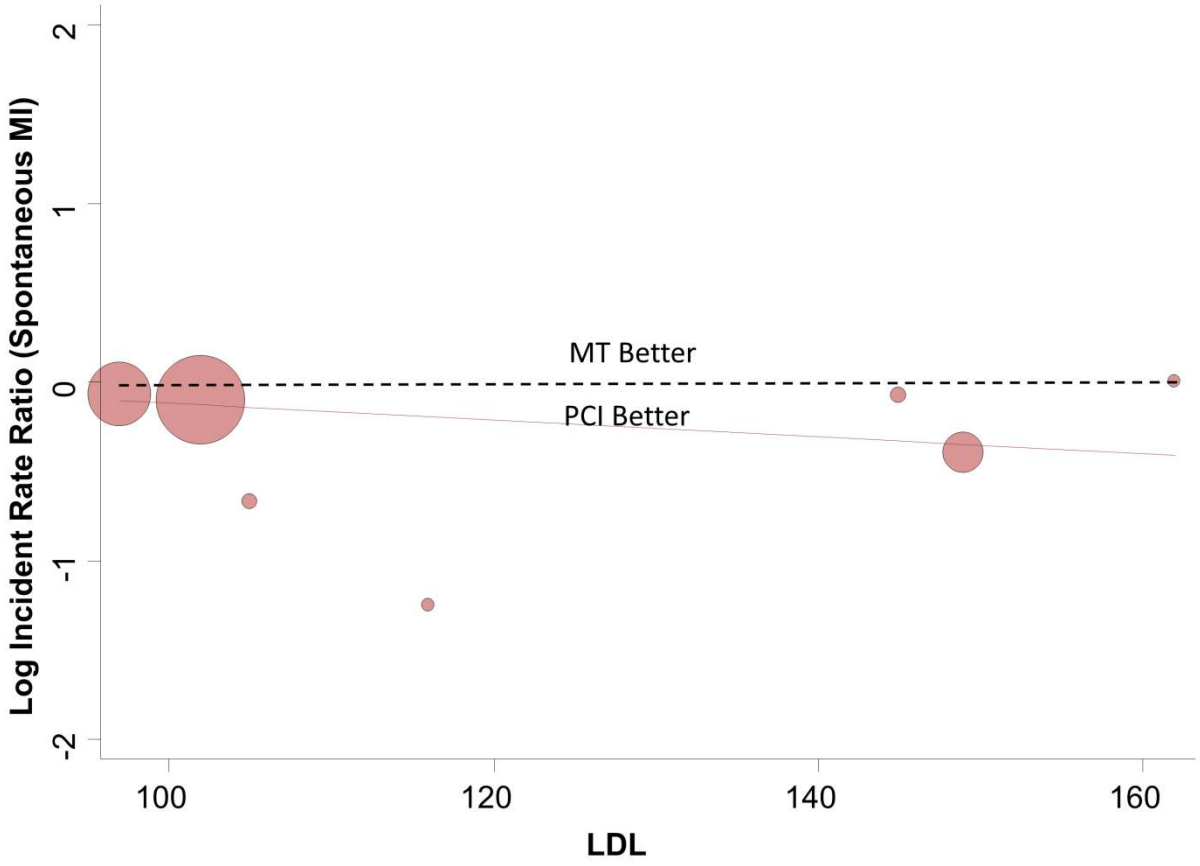
Supplemental Figure 3. Funnel plot for the outcome of all non-fatal MI



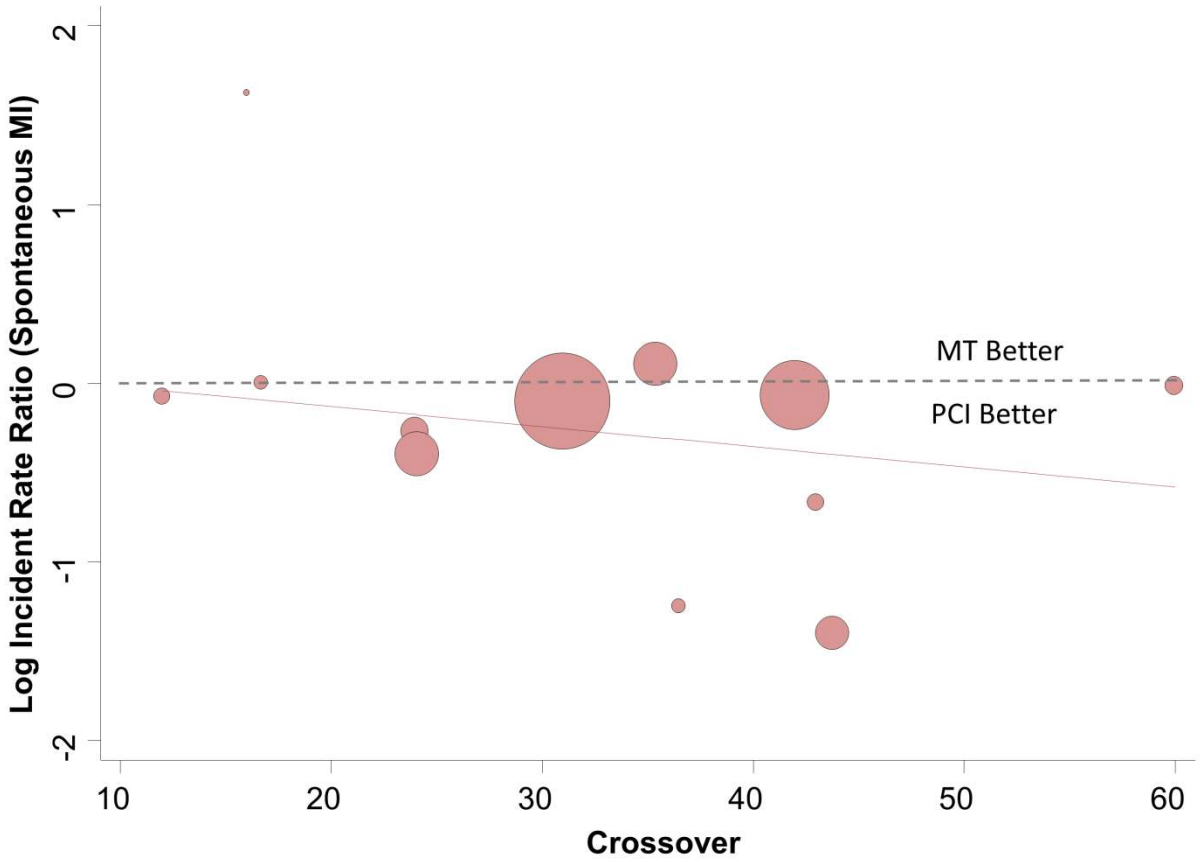
Supplemental Figure 4. Influence of percentage stents used in the PCI group on the incident rate ratio for the outcome of spontaneous MI.



Supplemental Figure 5. Influence of achieved LDL cholesterol levels in the OMT group on the incident rate ratio for the outcome of spontaneous MI.



Supplemental Figure 6. Influence of crossovers in the OMT group on the incident rate ratio for the outcome of spontaneous MI.



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Percutaneous Coronary Intervention Versus Optimal Medical Therapy for Prevention of Spontaneous Myocardial Infarction in Subjects With Stable Ischemic Heart Disease

Sripal Bangalore, Seema Pursnani, Sunil Kumar and Pantelis G. Bagos

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