

A Meta-analysis Update: Percutaneous Coronary Interventions

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It has been 31 years since the 1977 development of percutaneous transluminal angioplasty by Grüntzig^{1,2} for use in coronary arteries. The early diffusion of percutaneous coronary interventions (PCIs, previously percutaneous transluminal coronary angioplasty³) benefited from favorable Medicare pricing.^{4,5} Early Medicare payment for coronary angioplasty was based on coding to *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure code 36.0 (“removal of a coronary obstruction”), which was reimbursed through the inpatient hospital diagnosis related group system as open heart surgery (diagnosis related group 108), despite the lower costs of PCIs.⁶ An analysis by Sawi⁷ cites 1982 costs for coronary artery bypass graft (CABG) surgery as \$20,000 and costs for PCIs as \$3000. Zweifel⁸ notes that, while new technology lowers the unit cost of production among industry in healthcare, it drives up the total cost. The use of PCIs in the United States grew from 1800 cumulative procedures from June 1979 through May 1981, to 32,300 procedures in 1983, to more than 200,000 procedures in 1988. From 2000 through 2005, more than 7 million coronary artery angioplasties, arthroscopies, or stent insertions have been performed in the United States.⁹⁻¹⁴ Using the mean national Medicare hospital payment rate for fiscal 2006 of \$13,793, the procedures could represent hospital cost ranging from \$54 billion to \$97.4 billion. Estimates of national commercial insurance mean costs for PCIs, including physician fees, approximate \$24,400 per case, giving a total cost estimate of \$96 billion to \$170 billion for the 6-year period from 2000 to 2005. (The \$24,400 value is based on the BlueCross BlueShield of Tennessee treatment cost estimator. The treatment cost estimator is a collaborative project of Consortium Health Plans, BlueCross BlueShield Association, and Milliman USA. Based on the ClaimsQuest cost modeling system, the treatment cost estimates are episode treatment group-based. For the \$96-billion to \$170-billion estimate, there is considerable uncertainty surrounding the values. The source of the uncertainty is accounting for the number of procedures versus the number of patients; that is, a single patient could have both angioplasty and stent procedures performed within a single stay, for which there could be a single-case rate payment, a per diem rate-based payment, or a payment based on the fees for individual procedures and implanted stents.) Despite the high level of in-

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Objective: To update the most recent meta-analysis comparing percutaneous coronary interventions (PCIs) with medical therapy (MT) in patients having stable coronary artery disease (CAD) by including 2 new large trials that double the total number of patients.

Study Design: Meta-analysis was used to update previous meta-analyses of PCIs in stable CAD. Eleven previously analyzed randomized controlled trials (RCTs) and 2 new RCTs were included.

Methods: Summary estimates of relative risk (RR) are obtained by applying fixed-effects and random-effects models. Statistical tests for assessing between-study heterogeneity and biases are performed. Cumulative estimates and results from influence analysis are reported.

Results: No difference between PCIs and MT alone was found for risk of mortality. There was a 12% increase in the RR of cardiac death or myocardial infarction (MI) associated with PCIs, as well as a 22% increase in the RR of nonfatal MI associated with PCIs. Cumulative analysis favored MT over PCIs as early as 1997, but recent study results have increased confidence in this finding. Because of heterogeneity between studies, no certain conclusions are drawn for the use of PCIs in preventing follow-up PCI or coronary artery bypass graft surgery.

Conclusion: Recent RCTs comparing PCIs with conservative MT in stable CAD increase confidence in previous findings that the use of PCIs does not offer marginal benefit over that of the use of MT alone for mortality risk, cardiac death or MI, and nonfatal MI.

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■ **Table.** Summary Fixed-effects and Random-effects Estimates of Relative Risk (RR)^a

Outcome	Mantel-Haenszel Fixed-effects Model		DerSimonian and Laird Random-effects Model		χ^2 Statistic ^c
	Estimate (95% CI)	H ₀ : RR = 1.0 ^b	Estimate (95% CI)	H ₀ : RR = 1.0 ^b	
Death	0.97 (0.82-1.15)	0.38 (<i>P</i> = .70)	0.97 (0.82-1.15)	0.38 (<i>P</i> = .71)	10.53 (<i>P</i> = .48)
Cardiac death or MI	1.12 (0.99-1.27)	1.82 (<i>P</i> = .07)	1.13 (0.97-1.30)	1.60 (<i>P</i> = .11)	12.80 (<i>P</i> = .38)
Nonfatal MI	1.22 (1.04-1.44)	2.41 (<i>P</i> = .02)	1.21 (1.02-1.42)	2.22 (<i>P</i> = .03)	6.96 (<i>P</i> = .86)
Follow-up PCI or CABG surgery	0.81 (0.74-0.88)	4.98 (<i>P</i> = .02)	1.00 (0.80-1.26)	0.02 (<i>P</i> = .99)	47.79 (<i>P</i> < .001)

CABG indicates coronary artery bypass graft; CI, confidence interval; H₀, the null hypothesis; MI, myocardial infarction; PCI, percutaneous coronary intervention.
^aAmong 13 randomized controlled trials.^{21,22,36-46}
^b*P* values in parentheses are for the hypothesis test.
^c*P* values in parentheses are for the *Q* statistic test of homogeneity.

vestment and experience with this technology, the marginal benefit of use in stable coronary artery disease (CAD) remains controversial, with study results often in conflict.¹⁵⁻¹⁸ Two previous meta-analyses^{19,20} of randomized controlled trials (RCTs) of PCIs versus medical therapy (MT) have shown no marginal benefit for PCIs over that of MT alone in death rates, myocardial infarction (MI), or need for subsequent revascularization in patients with nonacute CAD. Since the publication of the most recent meta-analysis,²⁰ 2 large RCTs have been added to the literature,^{21,22} more than doubling the total number of patients studied. The results of these new studies potentially have an important role in the development of policy regarding PCIs. The new studies have been portrayed in the lay press as “landmark,”²³ implying that there is a historical change of course from the findings of previous studies. We update the meta-analysis of Katritsis and Ioannidis by including the 2 new studies^{21,22} and by addressing the consistency, heterogeneity, and bias of previous findings.

METHODS

We employed eligibility criteria, studied outcomes data, and meta-analytic methods of Katritsis and Ioannidis,²⁰ whose principal outcome measure was relative risk (RR). In addition to summary outcome measures and heterogeneity test results, we present cumulative estimates and influence analysis, and test for the existence of biases.

Relative risks across studies were combined using the Mantel-Haenszel fixed-effects model and the DerSimonian and Laird random-effects model.²⁴⁻²⁷ In general, both methods give greater weight to studies with smaller variances. Weighting is shown graphically in forest plots, in which the size of the box is proportional to study weight (which is also shown in the plots) and in which the center of the box represents the size of the

treatment effect estimated from that study (point estimate). The confidence interval (CI) for the treatment effect from each study is also shown. The pooled treatment effect is indicated by the middle of the diamond. An estimate less than 1.0 favors PCIs, while an estimate of 1.0 or greater favors MT alone. Influence analysis was performed by omitting 1 study at a time from the Mantel-Haenszel or DerSimonian and Laird model. A study is influential if, when omitted, the combined meta-analytic estimate differs significantly from that achieved when the study is included. Cumulative effects are shown in the cumulative-effects plot, in which the first circle represents the results of the first study only, while subsequent circles represent the weighted results of all previous studies in addition to the current study. Between-study heterogeneity was tested using χ^2 -based *Q* statistic. Publication and other biases were investigated using funnel plots²⁸ and formally using Egger’s regression asymmetry test.²⁹⁻³² We account for any biases detected by applying the “trim and fill” method developed by Duval and Tweedie.³³⁻³⁵

Problems in the computation of RR and standard errors of RR arise when a study contains no events (the meta-analysis studies^{21,22,36-46} are summarized in the **Table**). For example, Sievers et al⁴⁵ report no deaths in the intervention group, so that the estimated RR ratio is zero and its standard error cannot be estimated. To overcome this problem, we add 0.5 to each observed frequency (ie, to each cell of the 2 × 2 contingency table for the trial). When the treated and the control groups of the study contain zero events, presenting effect size estimates as RR ratios is meaningless. We have one such case (by Hambrecht et al⁴⁰) for death due to all causes, and we discard it from that portion of the meta-analysis.

The primary end points are the following clinical outcomes: death (due to all causes), cardiac death or MI, nonfatal MI, and follow-up procedures that include PCIs and CABG surgery.

RESULTS

There were 509 deaths (250 in the PCI group and 259 in the MT group), 855 patients had cardiac death or MI (452 in the PCI group and 403 in the MT group), 520 patients had nonfatal MI (287 in the PCI group and 233 in the MT group), and 1628 patients underwent follow-up PCIs or CABG surgery (726 in the PCI group and 902 in the MT group). Pooled estimates for the 13 RCTs^{21,22,36-46} are given in the Table.

No difference between PCIs and MT alone was found for risk of mortality. There was a 12% increase in the RR of cardiac death or MI associated with PCIs, as well as a 22% increase in the RR of nonfatal MI associated with PCIs.

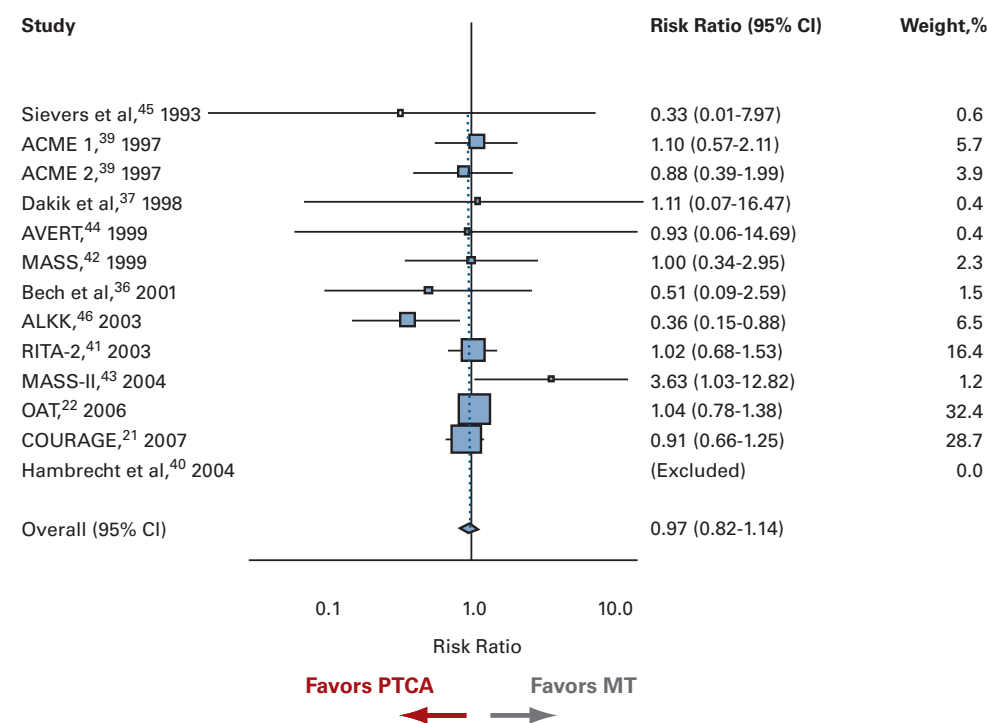
One trial, the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK),⁴⁶ reports an RR and a 95% CI that are below 1.0 for mortality (RR, 0.36; 95% CI, 0.15-0.88), while another trial, the Medicine, Angioplasty, or Surgery Study (MASS-II),⁴³ reports an RR and a 95% CI that are above 1.0 for mortality (RR, 3.63; 95% CI, 1.03-12.82). The remaining trials report RRs and CIs for mortality that include 1.0 (Figure 1). The pooled RR for mortality is 0.97 (95% CI, 0.82-1.14). For cardiac death or MI, the ALKK⁴⁶ reports an RR and a 95% CI that terminate at 1.0 from below, while the MASS-II⁴³ reports an RR and a 95% CI that terminate at 1.0 from above (Figure 2). The pooled RR for cardiac death or MI is 1.12 (95% CI, 0.99-1.27). No individual trial reports an RR and a CI that do not include 1.0 for nonfatal MI; the pooled RR is 1.22 (95% CI, 1.04-1.44) (Figure 3). Evidence from individual RR ratios is mixed for follow-up PCI or CABG surgery, with a pooled RR estimate of 1.00 (95% CI, 0.80-1.26) (Figure 4). Additional results are given in the online appendix (eAppendix; available at: www.ajmc.org).

DISCUSSION

This study adds to the current body of literature on PCIs by considering between-study heterogeneity, bias, consistency of outcomes among studies, inclusion of 2 recent large studies, and historical aspects of PCI acceptance by payers and healthcare providers. Consideration of these features affirms and increases confidence in the previous findings. We also find that contrary to perception, except for the first RCT,⁴⁵ cumulative effects support the finding that PCIs offer no marginal benefit over MT for the 4 outcomes studied herein. Consideration of how PCIs became covered by Medicare and were accepted by healthcare providers lends credence to the conclusion that PCIs provide no marginal benefit over MT alone. Policy may be further informed by these findings because they may prompt additional service review by payers, employers, and consumers in addition to providers.

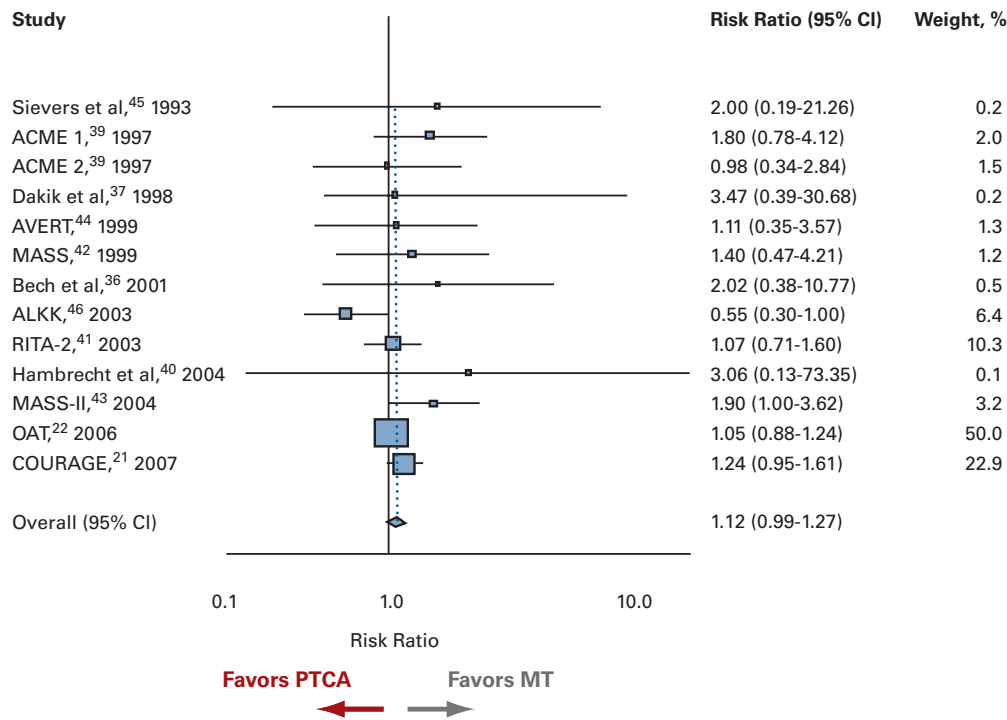
A meta-analysis by Katritsis and Ioannidis²⁰ of 11 RCTs comparing PCIs with conservative treatment in patients with stable CAD was updated to include 2 recent large trials.^{21,22} The following 4 outcomes were considered: (1) For death, the combined estimate of RR is 0.97, implying no difference

■ **Figure 1.** Forest Plot Comparing Percutaneous Transluminal Coronary Angioplasty (PTCA) versus Medical Therapy (MT) for Death (Fixed Effects) Among 13 Randomized Controlled Trials^{21,22,36-46}



CI indicates confidence interval.

■ **Figure 2.** Forest Plot Comparing Percutaneous Transluminal Coronary Angioplasty (PTCA) versus Medical Therapy (MT) for Cardiac Death or Myocardial Infarction (Fixed Effects) Among 13 Randomized Controlled Trials^{21,22,36-46}



CI indicates confidence interval.

between PCIs and MT. (2 and 3) For cardiac death or MI and for nonfatal MI, the combined estimates are greater than 1.0 (1.12 and 1.22, respectively), favoring MT. (4) When the clinical outcome is follow-up PCI or CABG surgery, random-effects estimation accounting for between-study heterogeneity demonstrates a wide 95% CI for the pooled RR, which prevents inferences about the superiority of PCIs versus MT. No evidence of between-study heterogeneity is found for death, cardiac death or MI, and nonfatal MI (Q statistics, $P = .48$, $P = .38$, and $P = .86$, respectively). Because of the small number of studies, the test of homogeneity has low power to detect excess variation (variation beyond sampling error) and cannot be interpreted as evidence of homogeneity. However, fixed-effects and random-effects estimates are remarkably close for these outcomes, implying the absence of between-study heterogeneity. The null hypothesis for unitary RR is rejected for nonfatal MI ($P < .05$).

The fixed-effects estimate of RR for follow-up PCI or CABG surgery in patients treated with PCIs compared with MT is 0.81. However, because of substantial between-study heterogeneity ($\chi^2 = 47.79$, $P < .01$), this estimate is unreliable. By ignoring between-study variability, the fixed-effects model underestimates the standard error of the summary estimate and

creates a misleadingly narrow CI. The substantial between-study variability is taken into account in the computation of the random-effects estimate (RR, 1.00) and is reflected in a wider 95% CI of 0.80 to 1.26. Consequently, no conclusions can be made based on the more conservative random-effects estimate. Four trials, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE),²¹ Occluded Artery Trial (OAT),²² Second Randomized Intervention Treatment of Angina (RITA-2),⁴¹ and ALKK,⁴⁶ favor PCIs, while MASS⁴² favors MT. Because the sources of heterogeneity are unclear, we cannot produce an overall estimate that is conclusive.

The 3 largest trials (RITA-2,⁴¹ COURAGE,²¹ and OAT²²) account for 77.5% of total weight for mortality, 83.2% for cardiac death or MI, 81.4% for nonfatal MI, all fixed-effects models, and 41.7% of the total weight for follow-up PCI or CABG surgery; a random-effects model was used because of substantial between-study heterogeneity. The ALKK⁴⁶ favors PCIs for the outcomes of death, cardiac death or MI, and follow-up PCI or CABG surgery, accounting for 6.5%, 6.4%, and 5.9%, respectively, of the total weight. The MASS-II⁴³ favors MT alone and represents 1.2% and 3.2% of the total weight for death and for cardiac death or MI, respectively. COURAGE,²¹ ALKK,⁴⁶ OAT,²² and RITA-2⁴¹ favor PCIs for follow-up PCI or CABG surgery, accounting for 41.7% of the total weight, while MASS⁴² favors MT, accounting for 7.5% of the total weight.

In cumulative analysis (Figure 5 and eAppendix), trials are presented in chronologic order from the earliest (Sievers et al⁴⁵ [1993]) to the most recent (COURAGE²¹ [2007]), and cumulative summary estimates through the publication of each study are shown at that study's publication date. Publication of the Veterans Affairs ACME Investigators trial in

1997 (ACME-2)³⁹ provided insight that there was unlikely to be a difference in performance between PCIs and MT alone for the 4 outcomes studied. The cumulative meta-analysis plot shows that, although the new trials (OAT²² and COURAGE²¹) have not changed the estimated effects of PCIs on mortality, they significantly reduce the CI for the pooled estimate. Increased confidence in the otherwise known findings established by the contributions of OAT²² and COURAGE²¹ may engender additional support for a policy cognizant of the lack of marginal benefit of PCIs over that of

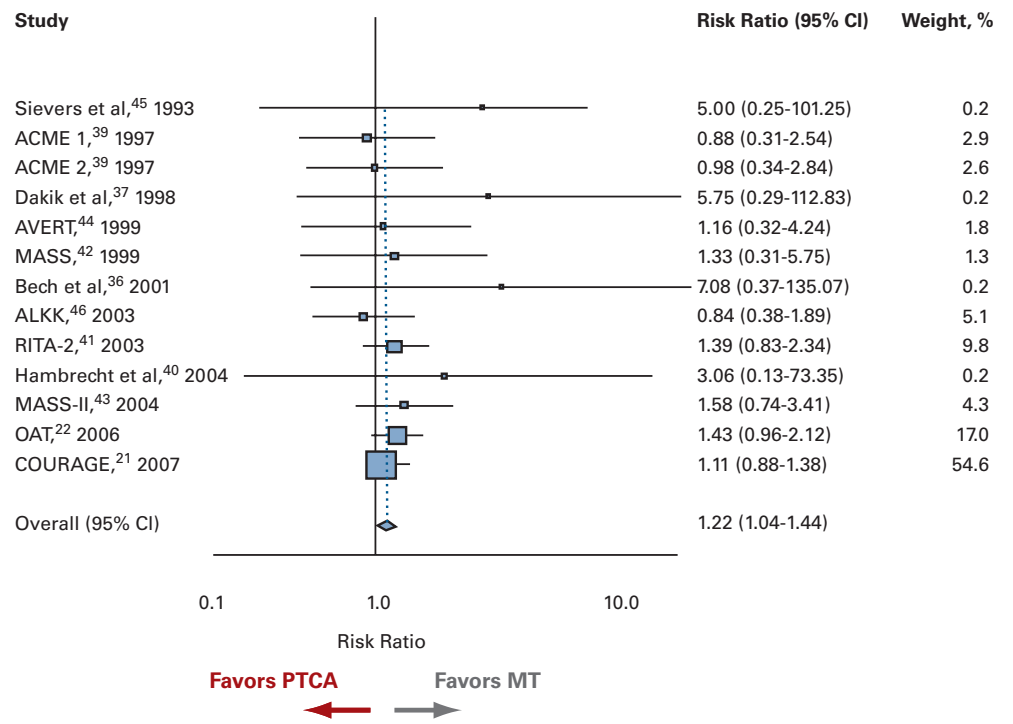
MT alone in nonacute cases. Cumulative analysis for cardiac death or MI, nonfatal MI, and follow-up PCI or CABG surgery also provides support for these conclusions.

The influence analysis shows that for death and for cardiac death or MI, the studies that have the largest influence are ALKK,⁴⁶ MASS-II,⁴³ OAT,²² and COURAGE.²¹ Omission of other studies makes little or no difference. Follow-up PCI or CABG surgery is dominated by the COURAGE²¹ trial.

Factors that may lead to a biased overall effect size estimate are summarized by Egger et al.²⁹ Publication bias (in which smaller studies showing negative effect [or no effect] of the treatment are less likely to get published) is usually the most serious concern, but we did not observe it herein. Quality bias was observed for nonfatal MI (funnel plots in eAppendix), which occurs when there are important differences in methodological quality between small and large studies. The lack of important information about disease and study characteristics in the study by Sievers et al⁴⁵ provides additional evidence for this explanation. Published as an abstract, the study provides no information about the enrollment period, percentage of men and subjects with diabetes mellitus, existence of symptoms, or mean ejection fraction.

The existence of biases in estimating the combined RR for nonfatal MI does not affect the conclusion that MT alone

Figure 3. Forest Plot Comparing Percutaneous Transluminal Coronary Angioplasty (PTCA) versus Medical Therapy (MT) for Nonfatal Myocardial Infarction (Fixed Effects) Among 13 Randomized Controlled Trials^{21,22,36-46}

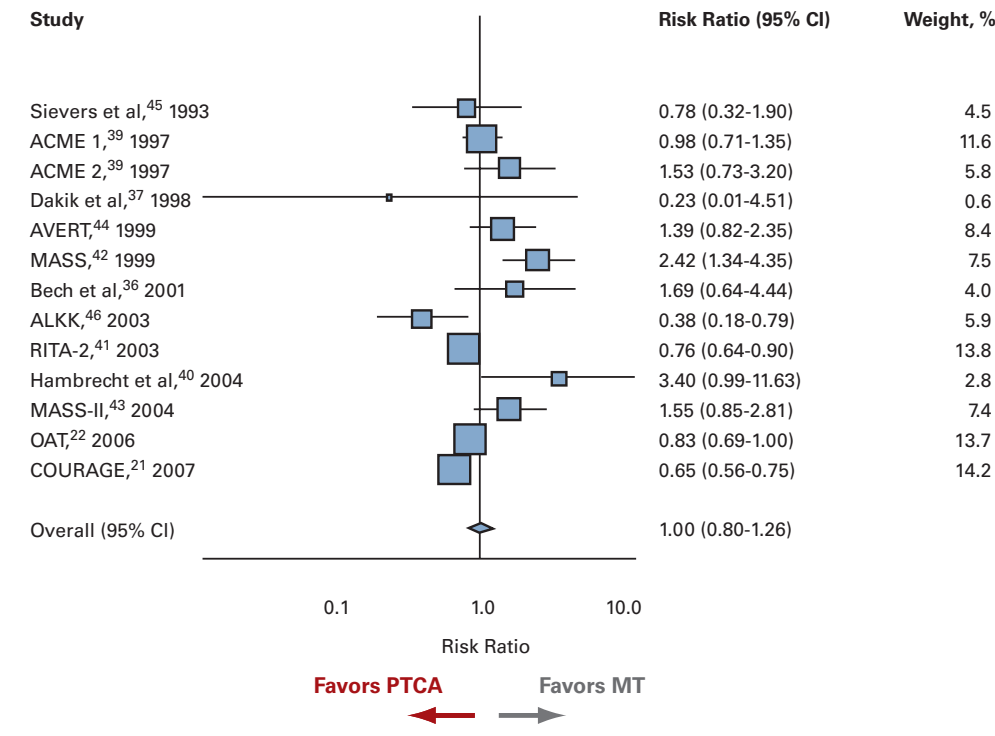


CI indicates confidence interval.

is favored compared with PCIs. To show this, we performed a sensitivity analysis that excluded the 4 studies^{36,37,40,45} with large RRs. The overall fixed-effects and random-effects estimate is 1.19 (95% CI, 1.01-1.41). The Duval and Tweedie nonparametric trim and fill method accounts for the bias by estimating the number and RRs of missing trials and adjusts the meta-analysis to incorporate the theoretical missing trials. The combined estimate using all 16 trials (13 actual trials and 3 theoretical trials created by the method of Duval and Tweedie) is 1.18 (95% CI, 1.01-1.40) (eAppendix). These estimates are close to those reported earlier, providing indirect evidence that bias did not seriously influence the summary estimate.

The US Food and Drug Administration released the first catheter marketed for PCIs from “investigational device exemption status” in late 1980, before publication of any RCTs demonstrating effectiveness.⁷ A 1983 survey of Medicare contractors to whom the coverage decision was delegated, also conducted before publication of any RCTs, found that 61.1% covered single-vessel PCIs, 19.2% covered PCIs of 2 or more vessels without qualification, and another 19.2% covered PCIs of 2 or more vessels with qualification.⁴⁷ The Medicare coverage policy was that single-coronary artery PCIs were covered, while PCIs of 2 or more coronary arter-

■ **Figure 4.** Forest Plot Comparing Percutaneous Transluminal Coronary Angioplasty (PTCA) versus Medical Therapy (MT) for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery (Random Effects) Among 13 Randomized Controlled Trials^{21,22,36-46}



CI indicates confidence interval.

ies were not covered, although procedure effectiveness and safety had not been established. As Medicare inpatient hospital payment transitioned from cost-based to prospective payment, the effect of the new prospective payment system on medical technology adoption was a major concern of the Office of Technology Assessment.⁴⁸ Technology was classified as the following 4 types: (1) cost-raising, quality-enhancing new technology; (2) operating cost-saving innovations; (3) capital cost-saving innovations; and (4) service or procedure disadoption. New diagnostic and therapeutic procedures “that reduce LOS [length of stay] or intensity of care” were classified as technology type 2. The diffusion of PCI technology occurred in response to prices set by the Centers for Medicare & Medicaid Services, then known as the Health Care Finance Administration (HCFA) for payment of Medicare cases. It is likely the appeal to the HCFA and other payers was that of an inexpensive substitute for CABG surgery. In 1982, Sawi⁷, on page 172, notes the following: “[M]ost private carriers reimburse for PTCA [percutaneous transluminal coronary angioplasty] to some extent either knowingly or otherwise. In some cases, the charges for PTCA are ‘buried’ in other, chargeable, items, such as catheter laboratory charges, coronary angiograms, etc.”

A possible explanation for HCFA’s action to approve the use of PCIs was the fear of discouraging technologic innovation as payment structures changed. Percutaneous coronary interventions were accepted without adequate science to support their use. Payers accepted them largely based on the potential of PCIs to save costs, and healthcare providers accepted them based on favorable pricing. After 2 decades of PCI use, science was able to inform practice. After 3 decades of use, it can be said with confidence that the evidence rejects the hypothesis that the use of PCIs in stable CAD has a

marginal benefit over that of MT alone. The downstream consequences of multiple decisions favoring PCIs, made without adequate science to support them, are the following: (1) The estimates of costs for PCIs are likely to have ranged from \$15 billion to \$28.5 billion in 2006. (2) It is unclear whether there will be adequate study in the near term to assess the value of PCIs in unstable CAD, although 3 studies (Medicine vs Angiography in Thrombolytic Exclusion [MATE],⁴⁹ Thrombolysis in Myocardial Ischemia (TIMI IIIB),⁵⁰ and Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital [VANQWISH])⁵¹ have shown no marginal benefit over that of MT alone. (3) The use of PCIs in stable CAD will not suddenly drop to zero; that is, investment without positive return in terms of health over that provided by MT alone will continue for a period. (4) The question of how the fixed costs invested to perform PCIs will be managed will be a much more difficult policy question to address than the decision to cover PCIs in the first place.

The policy implications of covering very expensive health technologies include the following: (1) the need to be able to quantify and compare effectiveness and costs, (2) an understanding of the ethical dimensions of equity and the transfer

of income from those who will receive the new technology, and (3) a consideration of the relative societal value of investing in the medical technology compared with, for example, investment in education. When such large sums are considered, the effect on other economic sectors, jobs, and overall global competitiveness in the face of such an investment must be added to the equation.

Our analysis is limited in that the relative effectiveness of PCIs in treating angina is not considered. The presence of bias and between-study heterogeneity limits our ability to draw certain conclusions for the use of

PCIs in preventing follow-up PCI or CABG surgery, although the evidence does not favor PCIs. The use of PCIs in unstable CAD is also not considered in the present analysis.

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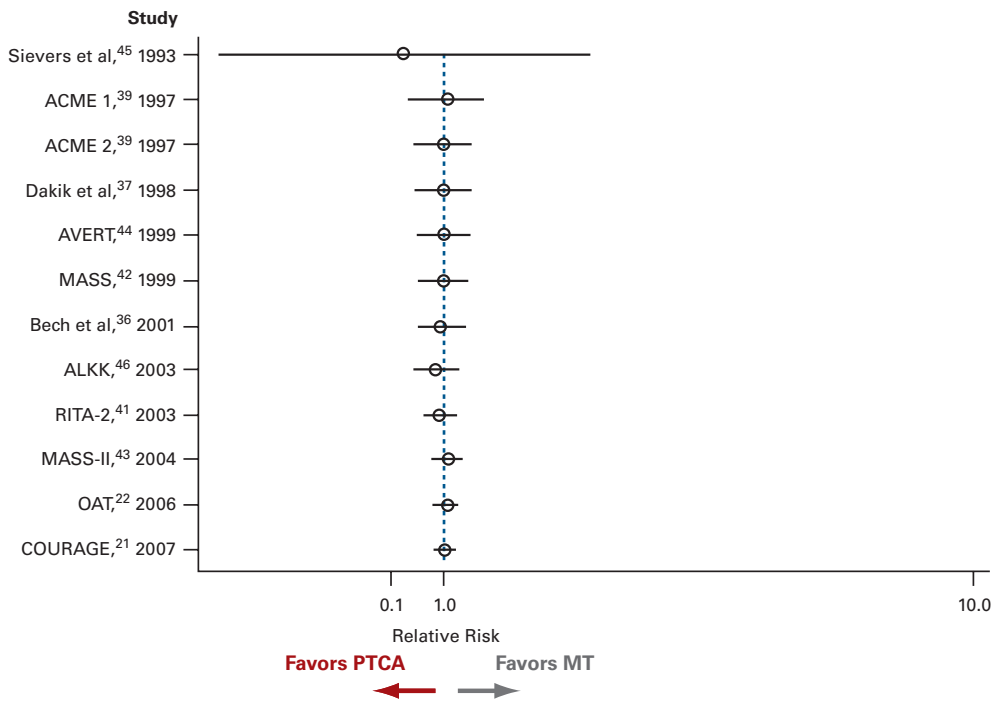
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■ **Figure 5.** Cumulative Fixed-effects Meta-analysis for Death Among 12 Randomized Controlled Trials^{21,22,36-46}



The results by Hambrecht et al⁴⁰ are excluded.

Take-away Points

The weight of evidence has not shown percutaneous coronary interventions (PCIs) to have marginal benefit in the treatment of stable coronary artery disease over that of medical therapy alone; recent large trials increase our confidence in this finding.

- Original favorable coverage decisions by Medicare were not based on whether PCIs provided marginal benefit over that of medical therapy; no randomized controlled trials were available for evaluation at that time.
- Early diffusion of PCIs was likely influenced by Medicare's decision to pay the same rate as open heart surgery and by early evaluation suggesting that PCIs could save money.

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■ eAppendix

This appendix contains additional results that supplement the article. [eTables 1-4](#) and [eFigures 1-5](#) augment the tables and figures in the main text.

Influence Analysis

The influence of individual studies on the summary effect estimate is shown in [eFigures 6-10](#). Pooled estimates are computed by omitting 1 study at a time from the computation. The omitted study is indicated on the left, and the summary statistics are given as confidence intervals (CIs) (with point estimates indicated by circles) and reflect the summary values exclusive of the omitted study. The full meta-analysis results (omitting none of the studies) are indicated by solid vertical lines. Although there is no formal test of influence, a study is influential if, when omitted, the combined meta-analysis estimate differs significantly from that achieved when the study is included. The test, as undertaken herein, is used to illustrate which studies have influenced the summary estimates of the meta-analysis.

The RR in COURAGE²¹ is 0.65, demonstrating a positive effect of angioplasties in reducing the rates of successive PCIs or CABG surgical procedures. As a result, omitting the study from the meta-analysis drives the pooled estimate (0.81 for fixed effects and 1.00 for random effects) toward larger values (0.90 for fixed effects and 1.08 for random effects). However, the influence of the study is larger when a fixed-effects model is applied: the point estimate of the omitted analysis lies outside the CI of the combined analysis. This finding is consistent with the fact that fixed-effects models place more weight on larger studies than random-effects models. The influence analysis results for fixed effects are also given in [eTable 5](#). The rows of the table represent the meta-analysis statistics of all studies except for the omitted study named in that row, and the full meta-analysis estimates (omitting none of the studies) are given as “combined” results in the last row of the table.

Bias

The graphical method of funnel plots is an informal way to explore for the existence of bias. In [eFigures 11-14](#), RRs from individual trials are represented against the standard error of RRs, with the horizontal line indicating the fixed-effects summary estimate. Ideally, the plot resembles a symmetric funnel. As the sample size increases, the underlying treatment effect is estimated more precisely. As a result, estimates from small trials are scattered more widely at the

right end of the plot, where the standard error is large. The spread of the estimates becomes narrower as we move to the left of the graph, where larger trials are represented.

An asymmetric funnel plot may be the result of biases. In the presence of publication bias (in which smaller studies showing negative effects [or no effect] of the treatment are less likely to be published), we would observe a blank space in the upper right corner of the funnel plot, reflecting the absence of small studies that favor MT. We do not observe such a pattern in any of our funnel plots ([eFigures 11-14](#)).

In contrast, in the funnel plot for nonfatal MI ([eFigure 12](#)), all small studies (Sievers et al,⁴⁵ Dakik et al,³⁷ Bech et al,³⁶ and Hambrecht et al⁴⁰) with weights of 0.2% each are located at the upper right corner and exhibit large RRs. This pattern may indicate important differences in methodological quality between small and large studies (quality bias).

Formally, we can detect funnel plot asymmetry using Egger regression asymmetry test, which regresses the standardized summary estimate (herein, the RR divided by its standard error) on the estimate’s precision (defined as the inverse of the standard error) and tests whether the intercept in this regression deviates significantly from zero. Rejection of the null hypothesis of zero intercept implies asymmetry. Egger plots ([eFigures 15-18](#)) are graphical representations of such regressions for all 4 outcomes. The standardized effect estimate is plotted against precision. If the CI around the intercept fails to include zero, funnel plot asymmetry is concluded. For death and for cardiac death or MI, zeros are included in CIs around the intercepts. For nonfatal MI and for follow-up PCI or CABG surgery, the intercepts are positive. The same information is given in [eTable 6](#).

Duval and Tweedie Trim and Fill Method

The blank space at the lower right corner of [eFigure 13](#) represents the absence of small trials favoring PCIs. The Duval and Tweedie nonparametric trim and fill method accounts for bias by estimating the numbers and RRs of missing trials and adjusts the meta-analysis to incorporate the theoretical missing trials. Therefore, 3 trials and their theoretical RRs are added to the meta-analysis, as shown in [eFigure 19](#).

Asymmetry in the funnel plot for follow-up PCI or CABG surgery ([eFigure 14](#)) is difficult to interpret given the small number of studies. There is no evidence of publication or quality bias. Asymmetry can be the result of several other factors, including true heterogeneity and pure chance. ■

■ **eAppendix Table 1A.** Patients and Disease Characteristics

Study	Enrollment	Age, mean, y	Male Sex, %	Diabetes Mellitus, %	1/2/3 Vessels, %	Follow-up, y
ACME-1, ³⁹ 1997	1987-1990	60	100	18	100/0/0	ND
ACME-2, ³⁹ 1997	1987-1990	60	100	18	0/100/0	ND
ALKK, ⁴⁶ 2003	1994-1997	58	87	16	100/0/0	4.7
AVERT, ⁴⁴ 1999	1995-1996	59	84	16	56/44/0	1.5
Bech et al, ³⁶ 2001	ND	61	64	12	66/28/6	2
COURAGE, ²¹ 2007	1999-2004	62	85	33	31/39/30	2.5-7
Dakik et al, ³⁷ 1998	1995-1996	53	59	ND	44/41/15	1
Hambrecht et al, ⁴⁰ 2004	1997-2001	61	100	23	58/27/15	1
MASS, ⁴² 1999	1988-1991	56	58	18	100/0/0	5
MASS-II, ⁴³ 2004	1995-2000	60	68	30	0/42/58	1
OAT, ²² 2006	2000-2005	59	78	21	Multivessel 18%	4
RITA-2, ⁴¹ 2003	1992-1996	58 (Median)	82	47	60/33/7	7
Sievers et al, ⁴⁵ 1993	ND	56	ND	0	100/0/0	2

ND indicates no data available.

■ **eAppendix Table 1B.** Patients and Disease Characteristics

Study	Mean Ejection Fraction, %	Prior Myocardial Infarction, %	Angina Symptoms
ACME-1, ³⁹ 1997	68	31	91%
ACME-2, ³⁹ 1997	67	41	82%
ALKK, ⁴⁶ 2003	ND	100	CCS I or II (100%)
AVERT, ⁴⁴ 1999	61	42	Asymptomatic (16.42%), CCS I (42.29%), CCS II (40.18%), CCS III (0.88%), CCS IV (0.29%)
Bech et al, ³⁶ 2001	65	25	CCS I (MT [12%], PTCA [12%]), CCS II (MT [45%], PTCA [57%]), CCS III (MT [35%], PTCA [27%]), CCS IV (MT [8%], PTCA [4%])
COURAGE, ²¹ 2007	61	38	CCS 0 (MT [13%], PTCA [12%]), CCS I (MT [30%], PTCA [30%]), CCS II (MT [37%], PTCA [36%]), CCS III (MT [19%], PTCA [23%]), missing (MT [$<1\%$], PTCA [$<1\%$])
Dakik et al, ³⁷ 1998	46	100	Inducible ischemia (100%)
Hambrecht et al, ⁴⁰ 2004	63	46	CCS I (35.6%), CCS II (59.4%), CCS III (5%)
MASS, ⁴² 1999	76	0	100%
MASS-II, ⁴³ 2004	67	41	ND
OAT, ²² 2006	48	11	22.5%
RITA-2, ⁴¹ 2003	ND	47	80% Reported symptoms at time of randomization. Almost all reported symptoms sometime earlier 16% admitted with symptoms 3 mo before randomization.
Sievers et al, ⁴⁵ 1993	ND	55	ND

CCS indicates the Canadian Cardiovascular Society Functional Classification of Angina; MT, medical treatment; ND, no data available; PTCA, percutaneous transluminal coronary angioplasty.

A Meta-analysis Update: Percutaneous Coronary Interventions

■ eAppendix Table 2. Numbers of Clinical Events in Trials of Percutaneous Coronary Interventions (PCI) vs Medical Therapy (MT)

Study	Death		Cardiac Death or MI		Nonfatal MI		Follow-up PCI or CABG Surgery	
	PTCA	MT	PTCA	MT	PTCA	MT	PTCA	MT
ACME-1, ³⁹ 1997	16/112	15/115	14/112	8/115	6/112	7/115	44/112	46/115
ACME-2, ³⁹ 1997	9/51	10/50	6/51	6/50	6/51	6/50	14/51	9/50
ALKK, ⁴⁶ 2003	6/149	17/151	14/149	26/151	10/149	12/151	9/149	24/151
AVERT ⁴⁴ 1999	1/177	1/164	6/177	5/164	5/177	4/164	30/177	20/164
Bech et al, ³⁶ 2001	2/90	4/91	4/90	2/91	3/90	0/91	10/90	6/91
COURAGE, ²¹ 2007	68/1149	74/1138	115/1149	92/1138	143/1149	128/1138	228/1149	348/1138
Dakik et al, ³⁷ 1998	1/19	1/22	3/19	1/22	2/19	0/22	0/19	2/22
Hambrech et al, ⁴⁰ 2004	0/50	0/51	1/50	0/51	1/50	0/51	10/50	3/51
MASS, ⁴² 1999	6/72	6/72	7/72	5/72	4/72	3/72	29/72	12/72
MASS-II, ⁴³ 2004	11/205	3/203	25/205	13/203	16/205	10/203	25/205	16/203
OAT, ²² 2006	87/1082	84/1084	211/1082	202/1084	57/1082	40/1084	170/1082	205/1084
RITA-2, ⁴¹ 2003	43/504	43/514	44/504	42/514	32/504	23/514	150/504	202/514
Sievers et al, ⁴⁵ 1993	0/44	1/44	2/44	1/44	2/44	0/44	7/44	9/44
Total	250/3704	259/3699	452/3704	403/3699	287/3704	233/3699	726/3704	902/3699

CABG indicates coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

■ **eAppendix Table 3A.** Relative Risks of Percutaneous Transluminal Coronary Angioplasty vs Medical Therapy for Major Outcomes

Study	Estimate (95% Confidence Interval)	
	Death	Cardiac Death or MI
ACME-1, ³⁹ 1997	1.10 (0.57-2.11)	1.80 (0.78-4.12)
ACME-2, ³⁹ 1997	0.88 (0.39-1.99)	0.98 (0.34-2.84)
ALKK, ⁴⁶ 2003	0.36 (0.15-0.88)	0.55 (0.30-1.00)
AVERT, ⁴⁴ 1999	0.93 (0.58-14.69)	1.11 (0.35-3.57)
Bech et al, ³⁶ 2001	0.51 (0.09-2.69)	2.02 (0.38-10.77)
COURAGE, ²¹ 2007	0.91 (0.66-1.25)	1.24 (0.95-1.61)
Dakik et al, ³⁷ 1998	1.11 (0.74-16.47)	3.47 (0.39-30.68)
Hambrecht et al, ⁴⁰ 2004	Excluded	3.06 (0.13-73.35)
MASS, ⁴² 1999	1.00 (0.34-2.95)	1.40 (0.47-4.21)
MASS-II, ⁴³ 2004	3.63 (1.03-12.82)	1.90 (1.00-3.62)
OAT, ²² 2006	1.04 (0.78-1.38)	1.05 (0.88-1.24)
RITA-2, ⁴¹ 2003	1.02 (0.68-1.53)	1.07 (0.71-1.60)
Sievers et al, ⁴⁵ 1993	0.33 (0.01-7.97)	2.00 (0.19-21.26)

MI indicates myocardial infarction.

■ **eAppendix Table 3B.** Relative Risks of Percutaneous Transluminal Coronary Angioplasty vs Medical Therapy for Major Outcomes

Study	Estimate (95% Confidence Interval)	
	Nonfatal MI	Follow-up PCI or CABG Surgery
ACME-1, ³⁹ 1997	0.88 (0.31-2.54)	0.98 (0.71-1.35)
ACME-2, ³⁹ 1997	0.98 (0.34-2.84)	1.53 (0.73-3.20)
ALKK, ⁴⁶ 2003	0.84 (0.38-1.89)	0.38 (0.18-0.79)
AVERT, ⁴⁴ 1999	1.16 (0.32-4.24)	1.39 (0.82-2.35)
Bech et al, ³⁶ 2001	7.08 (0.37-135.07)	1.69 (0.64-4.44)
COURAGE, ²¹ 2007	1.11 (0.88-1.38)	0.65 (0.56-0.75)
Dakik et al, ³⁷ 1998	5.75 (0.29-112.83)	0.23 (0.12-4.51)
Hambrecht et al, ⁴⁰ 2004	3.06 (0.13-73.35)	3.40 (0.99-11.63)
MASS, ⁴² 1999	1.33 (0.31-5.75)	2.42 (1.34-4.35)
MASS-II, ⁴³ 2004	1.58 (0.74-3.41)	1.55 (0.85-2.81)
OAT, ²² 2006	1.43 (0.96-2.12)	0.83 (0.69-1.00)
RITA-2, ⁴¹ 2003	1.39 (0.83-2.34)	0.76 (0.64-0.90)
Sievers et al, ⁴⁵ 1993	5.00 (0.25-101.25)	0.78 (0.32-1.90)

CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

■ **eAppendix Table 4.** Cumulative Estimates of Relative Risk

Study	Death		Cardiac Death or MI		Nonfatal MI		Follow-up PCI or CABG Surgery	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects
Sievers et al, ⁴⁵ 1993	0.333	0.333	2.000	2.000	5.000	5.000	0.778	0.778
ACME-1, ³⁹ 1997	1.064	1.064	1.819	1.819	1.334	2.690	0.959	0.959
ACME-2, ³⁹ 1997	0.994	0.994	1.524	1.524	1.168	1.626	1.040	1.046
Dakik et al, ³⁷ 1998	0.998	0.998	1.675	1.743	1.427	2.582	1.033	1.033
AVERT, ⁴⁴ 1999	0.996	0.996	1.566	1.575	1.365	2.086	1.111	1.111
MASS, ⁴² 1999	0.997	0.997	1.526	1.527	1.360	1.853	1.306	1.394
Bech et al, ³⁶ 2001	0.964	0.964	1.564	1.564	1.567	2.584	1.325	1.431
ALKK, ⁴⁶ 2003	0.852	0.852	1.190	1.364	1.332	2.178	1.246	1.289
RITA-2, ⁴¹ 2003	0.933	0.933	1.135	1.245	1.358	1.877	0.952	1.202
Hambrecht et al, ⁴⁰ 2004	Excluded	Excluded	1.149	1.278	1.378	1.927	0.980	1.355
MASS-II, ⁴³ 2004	1.059	1.118	1.264	1.396	1.412	1.804	1.007	1.373
OAT, ²² 2006	1.049	1.086	1.117	1.284	1.418	1.643	0.949	1.282
COURAGE, ²¹ 2007	1.010	1.043	1.145	1.245	1.248	1.486	0.845	1.186

CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

■ **eAppendix Table 5.** Influence Analysis (Fixed Effects) Relative Risks With Studies Omitted

Omitted Study	Death	Cardiac Death or MI	Nonfatal MI	Follow-up PCI or CABG Surgery
Sievers et al, ⁴⁵ 1993	0.972	1.120	1.216	0.806
ACME-1, ³⁹ 1997	0.960	1.109	1.234	0.796
ACME-2, ³⁹ 1997	0.971	1.124	1.230	0.798
Dakik et al, ³⁷ 1998	0.967	1.117	1.215	0.807
AVERT, ⁴⁴ 1999	0.968	1.123	1.225	0.792
MASS, ⁴² 1999	0.967	1.119	1.223	0.784
Bech et al, ³⁶ 2001	0.975	1.118	1.212	0.800
ALKK, ⁴⁶ 2003	1.010	1.162	1.244	0.817
RITA-2, ⁴¹ 2003	0.958	1.129	1.206	0.819
Hambrecht et al, ⁴⁰ 2004	0.968	1.120	1.220	0.797
MASS-II, ⁴³ 2004	0.937	1.096	1.208	0.792
OAT, ²² 2006	0.935	1.199	1.182	0.798
COURAGE, ²¹ 2007	0.991	1.088	1.365	0.905
Combined	0.968	1.123	1.224	0.805

CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

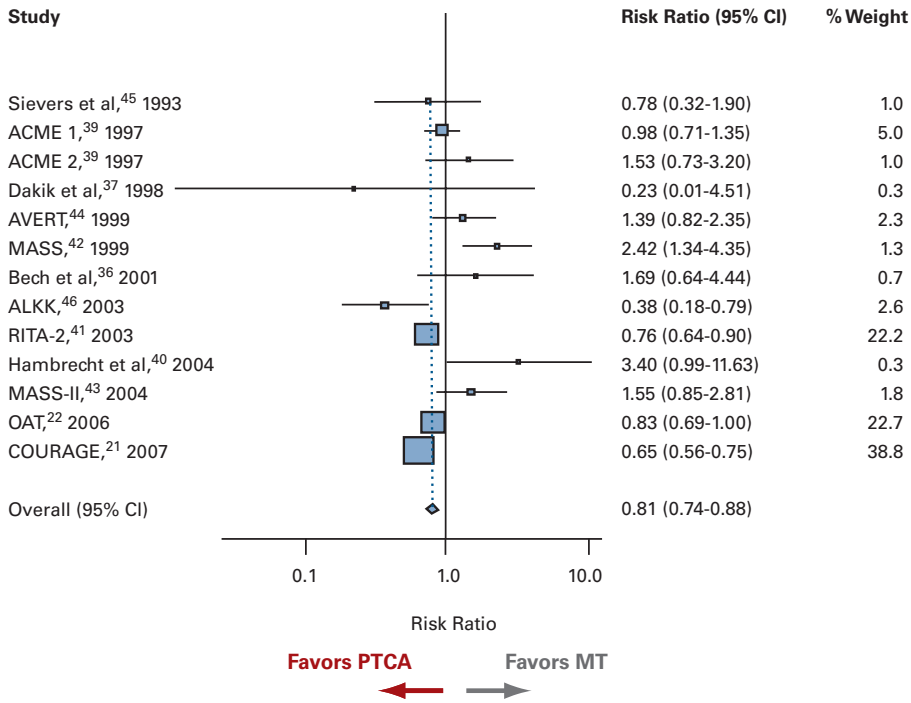
■ **eAppendix Table 6.** Egger Test for Publication Bias (Standardized Effect)

Variable	Coefficient (SE)	t Statistic	Pr > t Statistic (95% Confidence Interval)
Death			
Slope	0.95 (0.20)	4.83	0.001 (0.51 to 1.38)
Bias	0.27 (0.66)	0.41	0.692 (-1.20 to 1.74)
Cardiac Death or MI			
Slope	0.97 (0.11)	9.07	0.000 (0.74 to 1.21)
Bias	1.03 (0.47)	2.20	0.050 (0.00 to 2.05)
Nonfatal MI			
Slope	0.89 (0.18)	5.10	0.000 (0.51 to 1.28)
Bias	1.58 (0.58)	2.74	0.019 (0.31 to 2.84)
Follow-up PCI or CABG Surgery			
Slope	0.56 (1.33)	4.20	0.001 (0.27 to 0.85)
Bias	2.37 (0.84)	2.82	0.017 (0.52 to 4.22)

CABG indicates coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; Pr, probability.

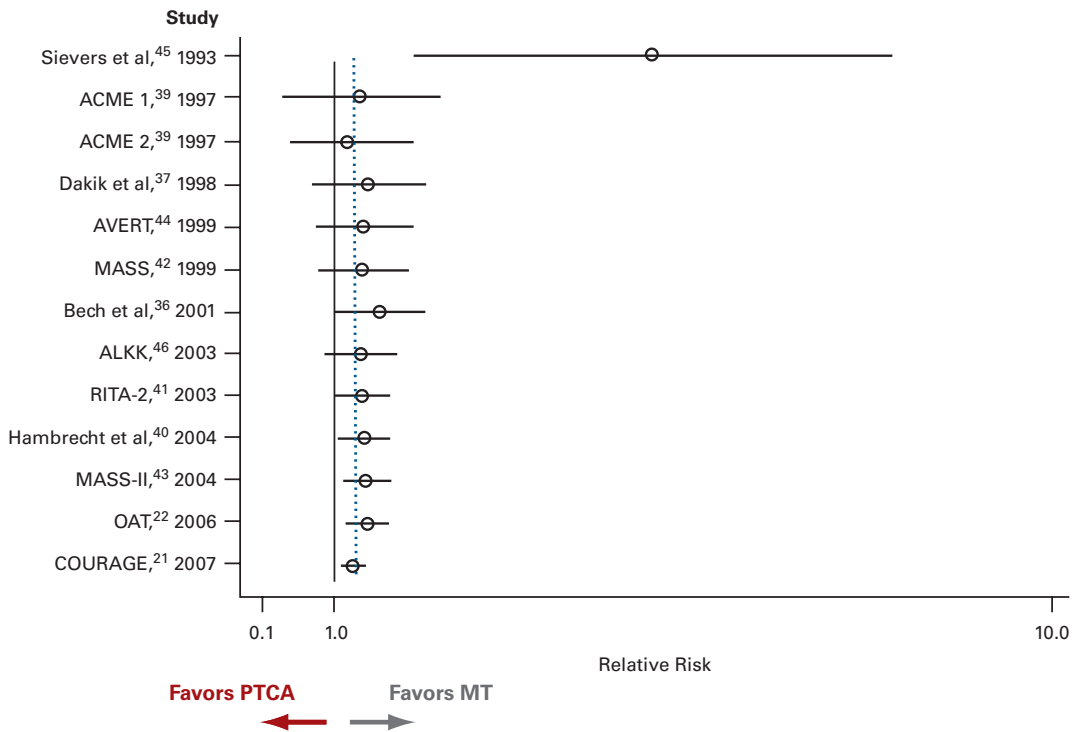
A Meta-analysis Update: Percutaneous Coronary Interventions

■ eAppendix Figure 1. Forest Plot Comparing Percutaneous Transluminal Coronary Angioplasty (PTCA) vs Medical Therapy (MT) for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery (Fixed Effects)



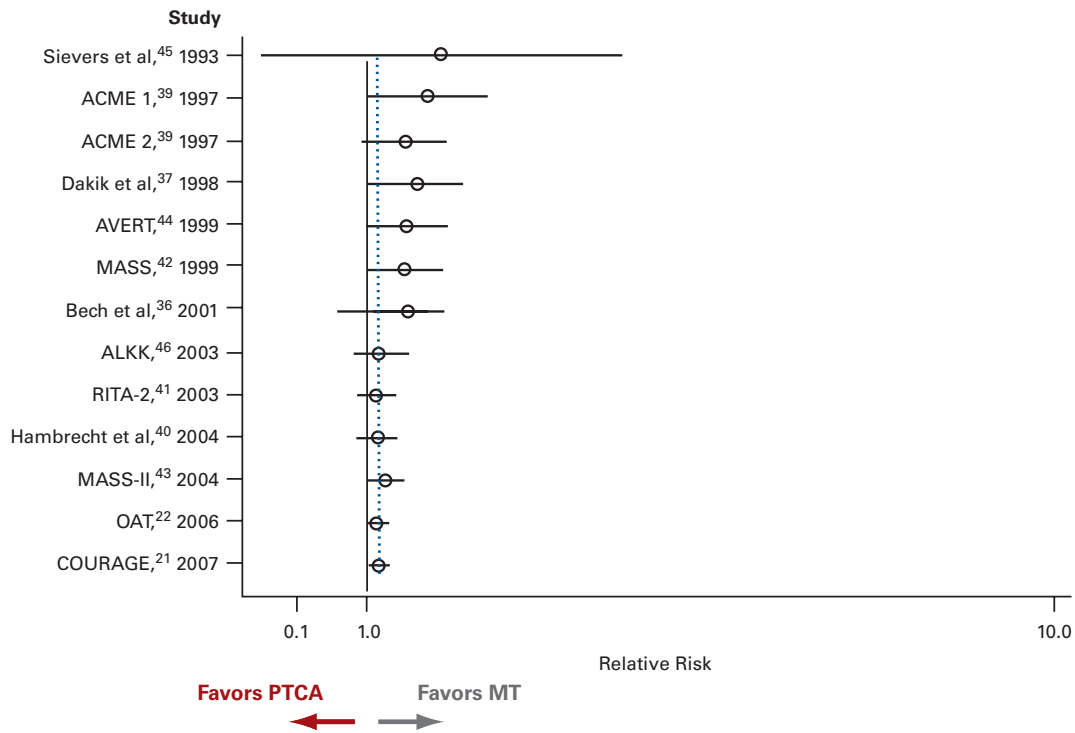
CI indicates confidence interval.

■ eAppendix Figure 2. Cumulative Fixed-effects Meta-analysis for Nonfatal Myocardial Infarction



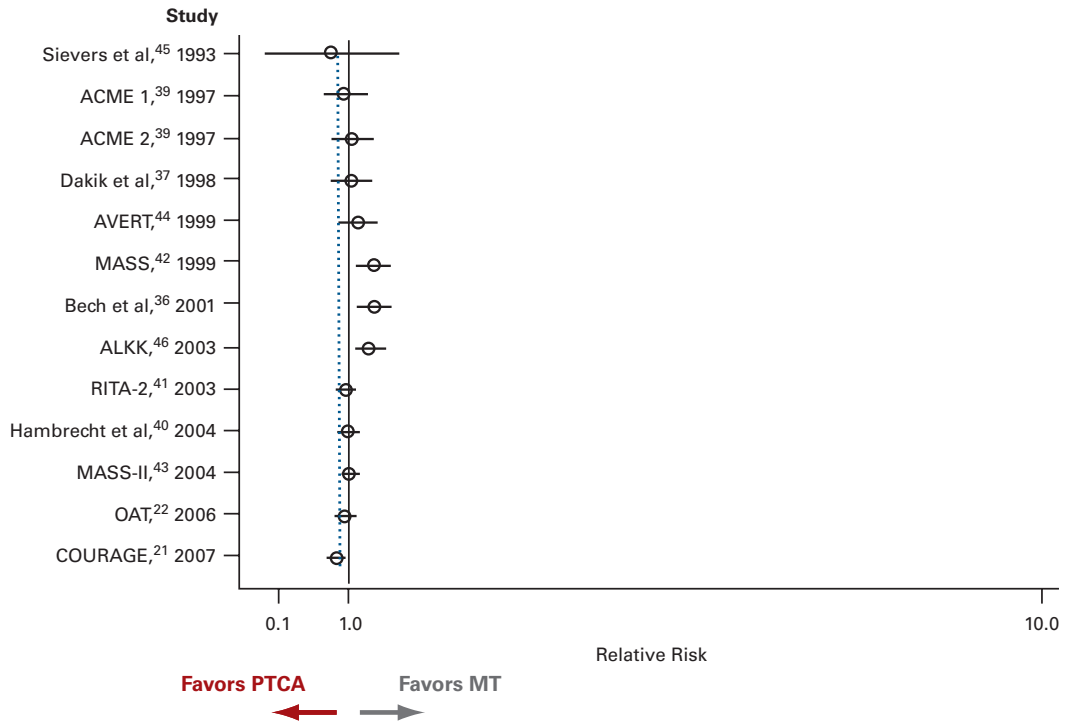
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

■ **eAppendix Figure 3.** Cumulative Fixed-effects Meta-analysis for Cardiac Death or Myocardial Infarction



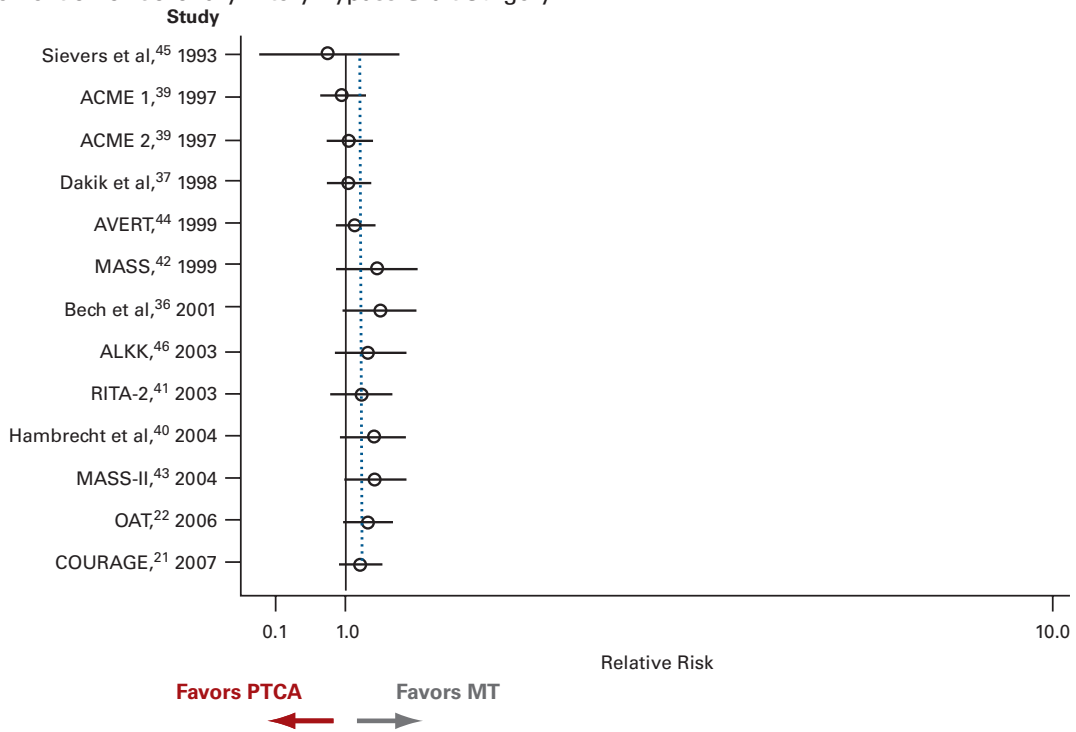
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

■ **eAppendix Figure 4.** Cumulative Fixed-effects Meta-analysis for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery



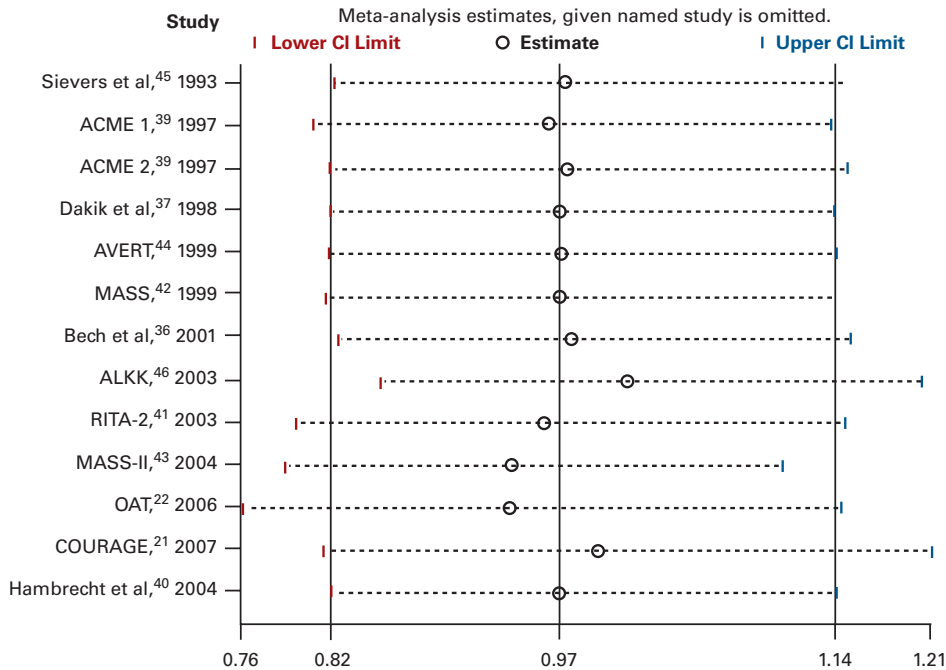
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

eAppendix Figure 5. Cumulative Random-effects Meta-analysis for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery



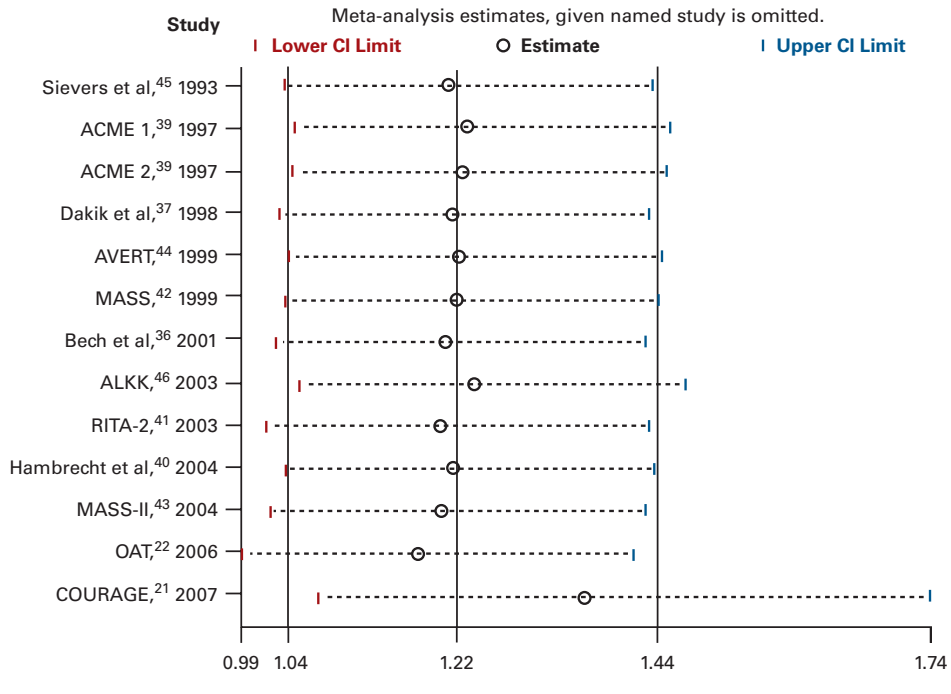
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

eAppendix Figure 6. Influence Analysis for Death (Fixed Effects)

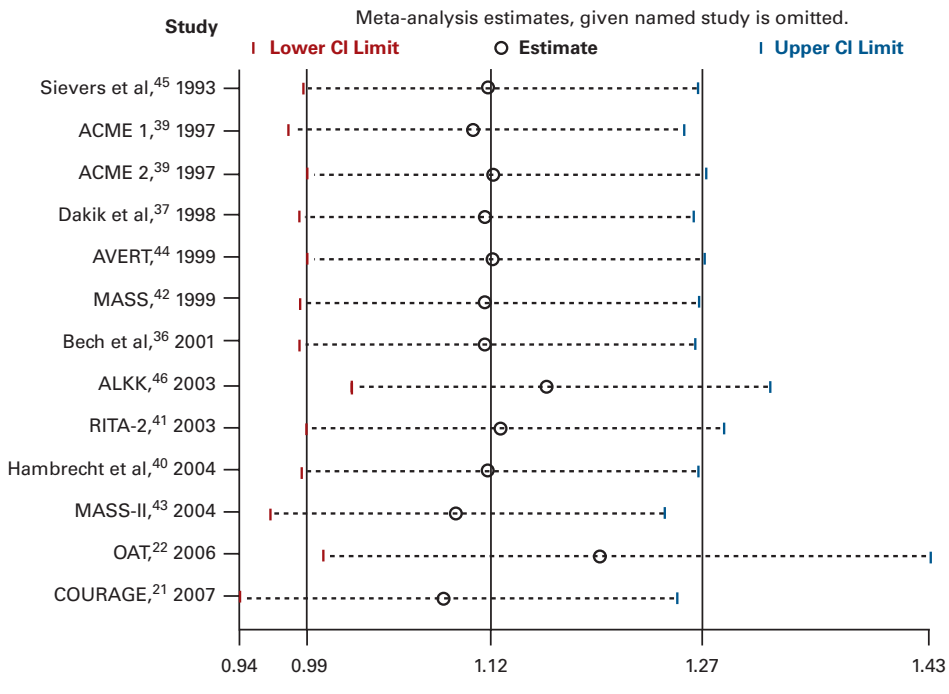


CI indicates confidence interval.

■ **eAppendix Figure 7.** Influence Analysis for Nonfatal Myocardial Infarction (Fixed Effects)

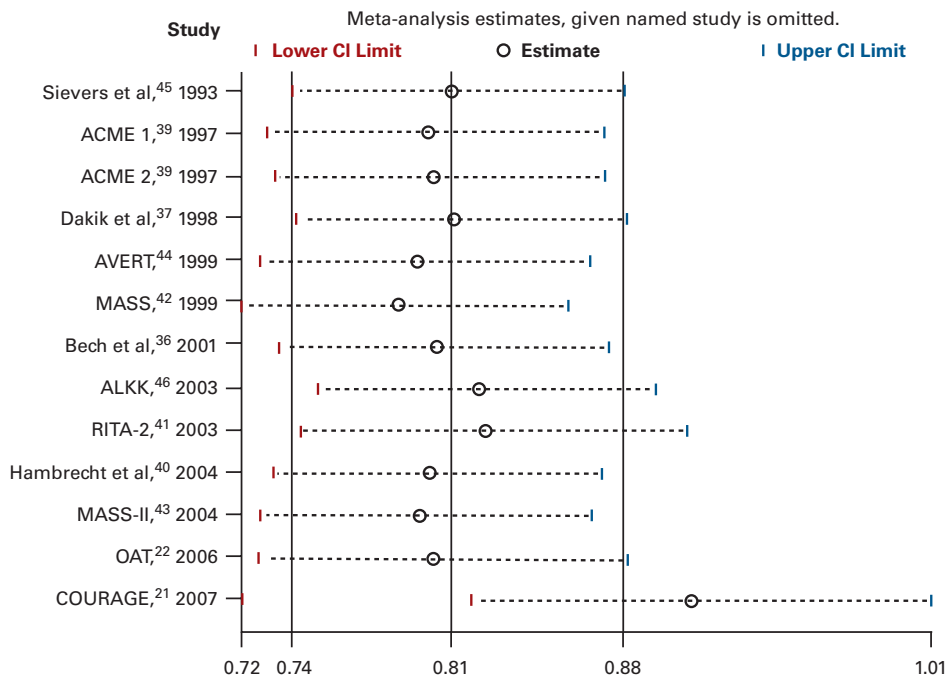


■ **eAppendix Figure 8.** Influence Analysis for Cardiac Death or Myocardial Infarction (Fixed Effects)



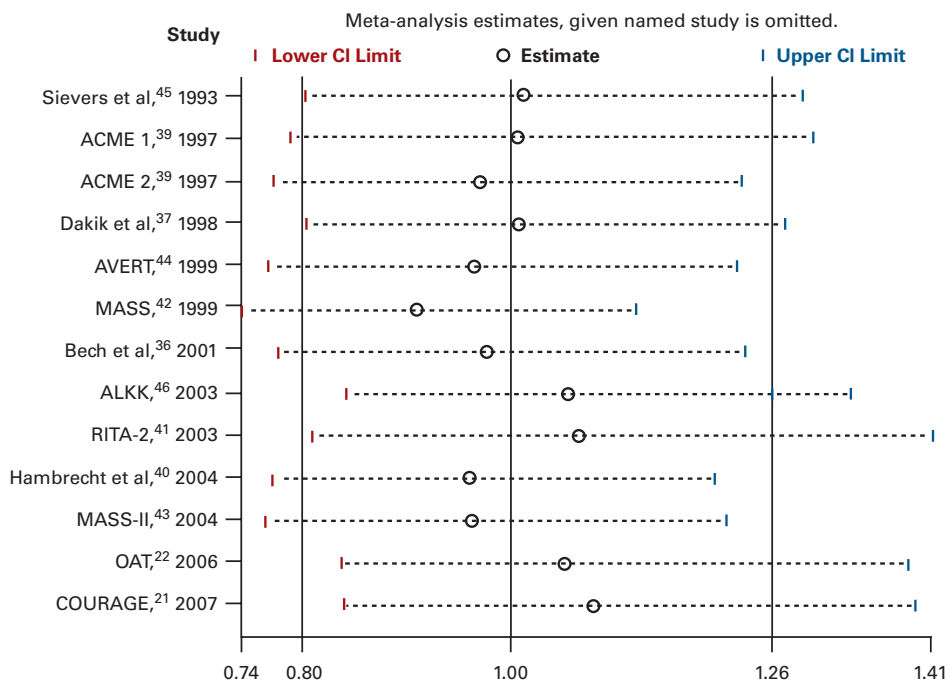
A Meta-analysis Update: Percutaneous Coronary Interventions

■ **eAppendix Figure 9.** Influence Analysis for Follow-up Percutaneous Coronary Intervention or Percutaneous Transluminal Coronary Angioplasty (Fixed Effects)



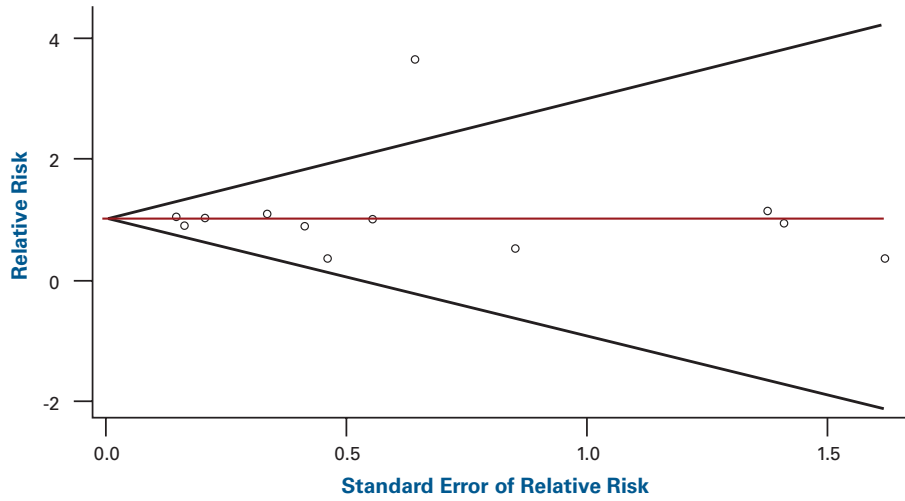
CI indicates confidence interval.

■ **eAppendix Figure 10.** Influence Analysis for Follow-up Percutaneous Coronary Intervention or Percutaneous Transluminal Coronary Angioplasty (Random Effects)

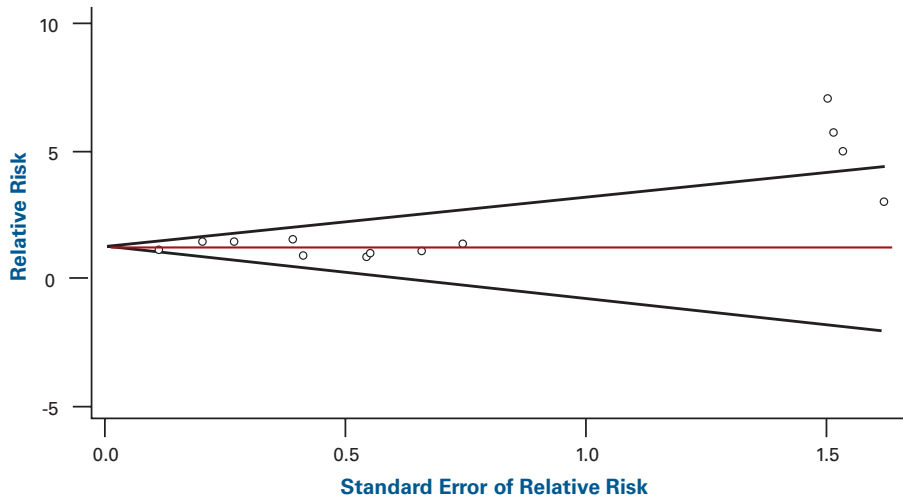


CI indicates confidence interval.

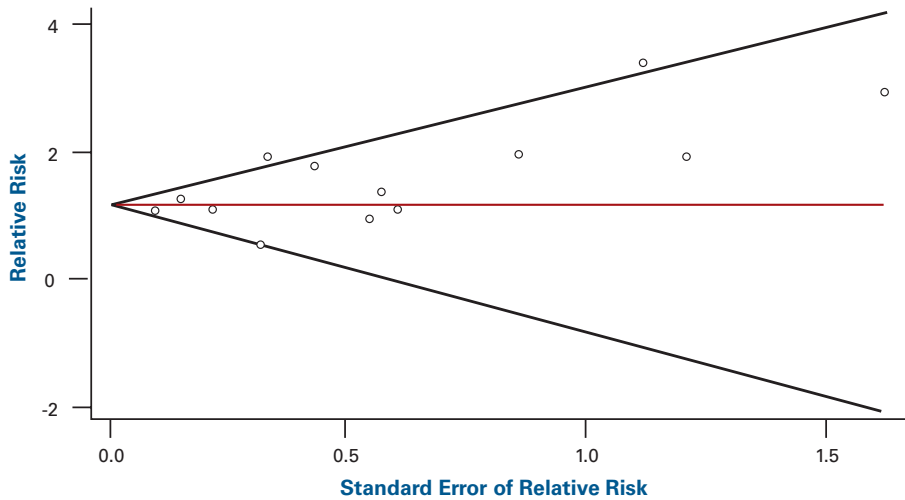
■ **eAppendix Figure 11.** Begg Funnel Plot With Pseudo 95% Confidence Limits for Death



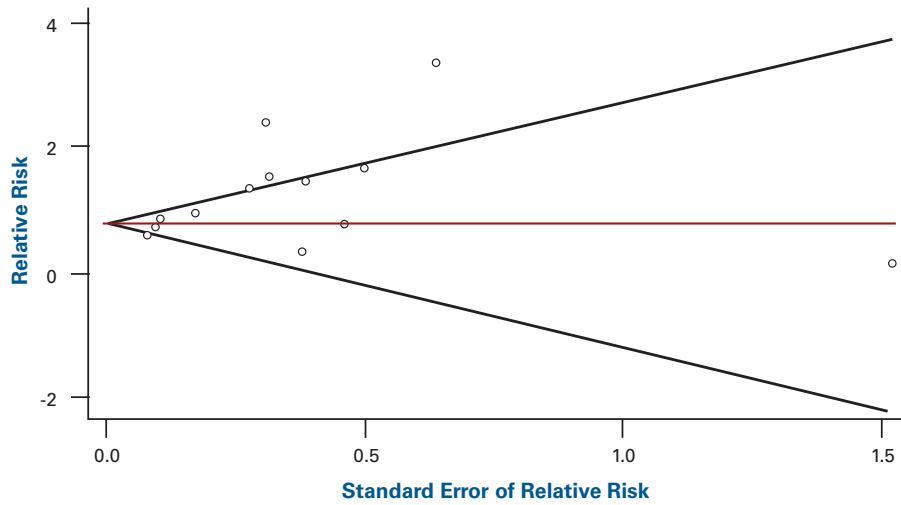
■ **eAppendix Figure 12.** Begg Funnel Plot With Pseudo 95% Confidence Limits for Nonfatal Myocardial Infarction



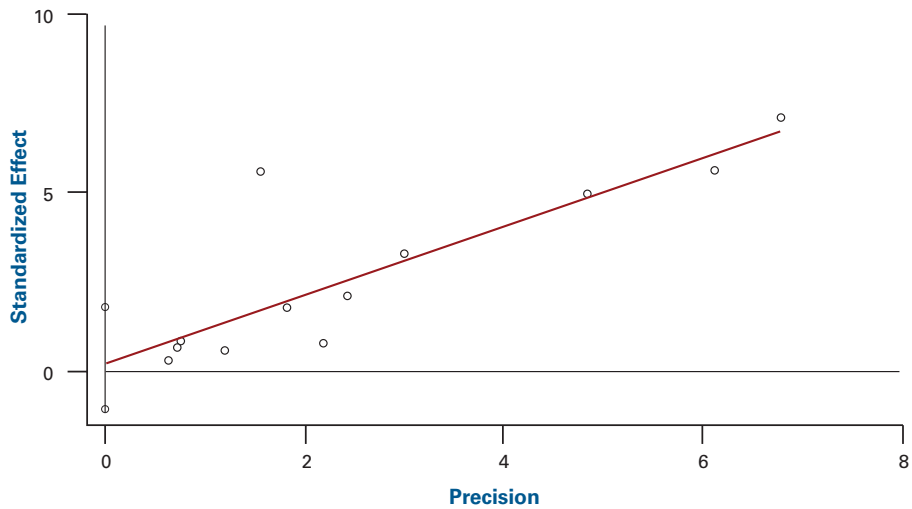
■ **eAppendix Figure 13.** Begg Funnel Plot With Pseudo 95% Confidence Limits for Cardiac Death or Myocardial Infarction



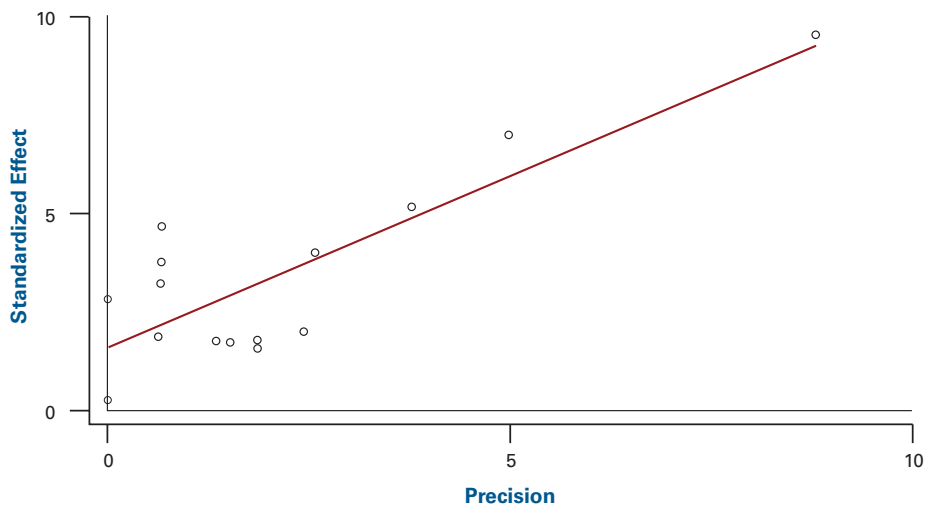
■ **eAppendix Figure 14.** Begg Funnel Plot for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery



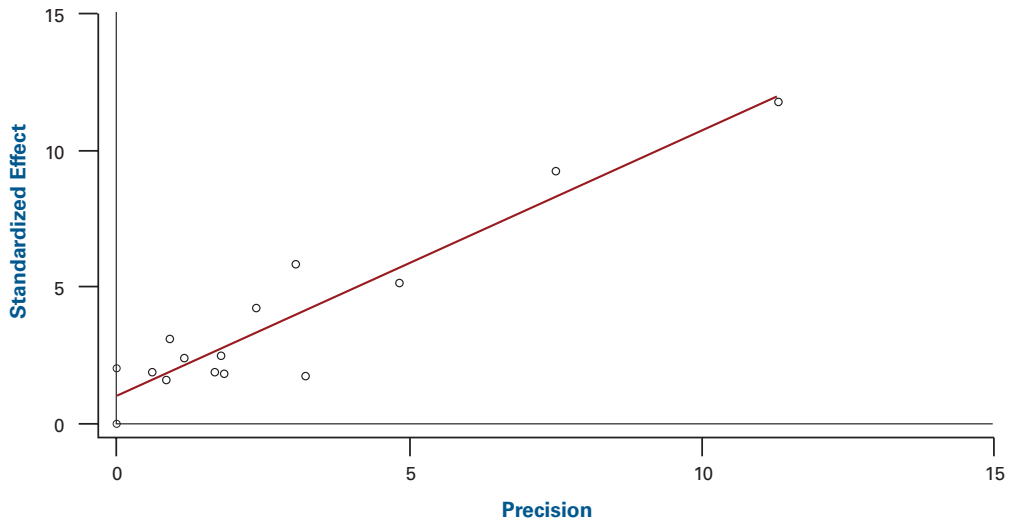
■ **eAppendix Figure 15.** Egger Publication Bias Plot for Death



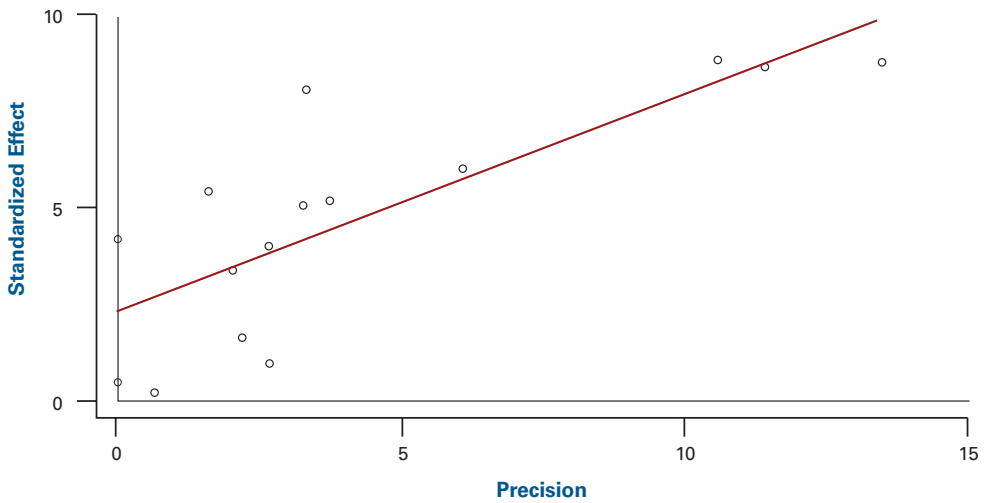
■ **eAppendix Figure 16.** Egger Publication Bias Plot for Nonfatal Myocardial Infarction



■ **eAppendix Figure 17.** Egger Publication Bias Plot for Cardiac Death or Myocardial Infarction



■ **eAppendix Figure 18.** Egger Publication Bias Plot for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery



■ **eAppendix Figure 19.** Duval and Tweedie Trim and Fill Method for Nonfatal Myocardial Infarction (Filled Funnel Plot With Pseudo 95% Confidence Limits)

