

■ 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
Hambrecht 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.

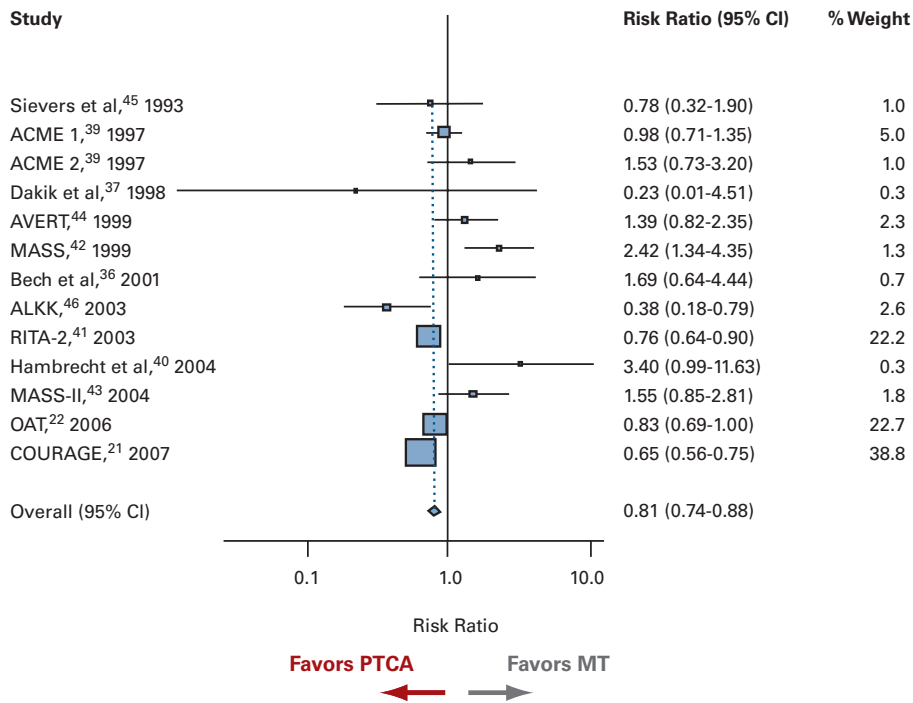
■ **eAppendix Table 6.** Egger Test for Publication Bias (Standardized Effect)

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.

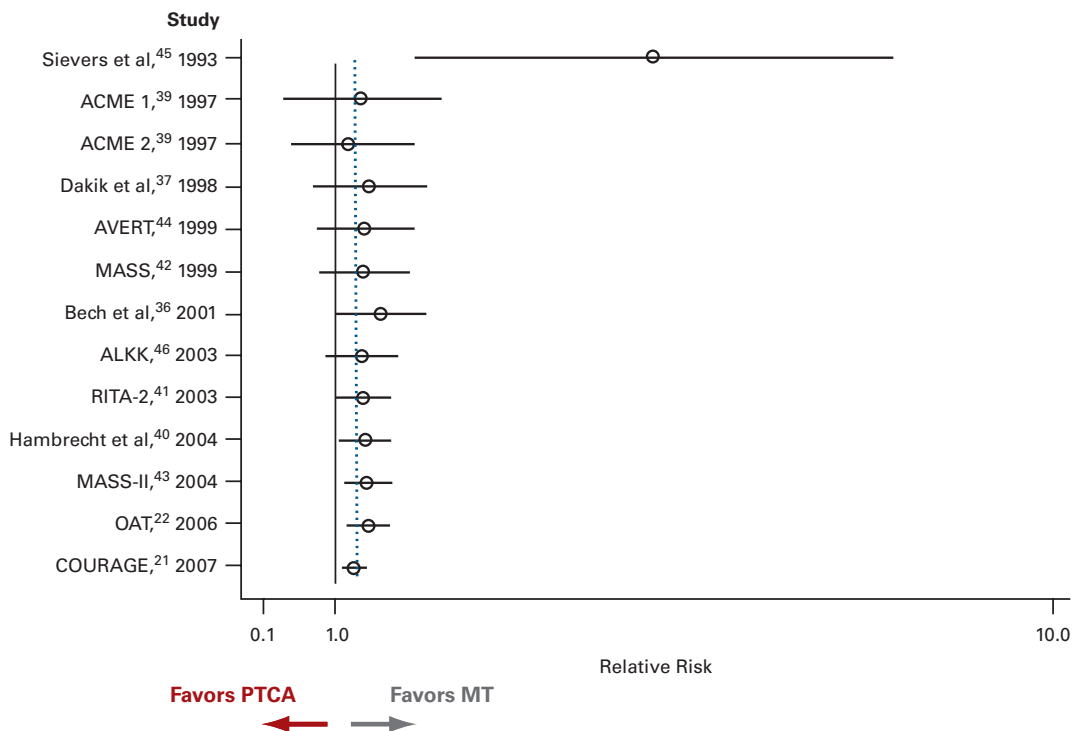
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■ eAppendix Figure 1. Forest Plot Comparing Percutaneous Transluminal Coronary Angioplasty (PTCA) vs Medical Therapy (MT) for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery (Fixed Effects)



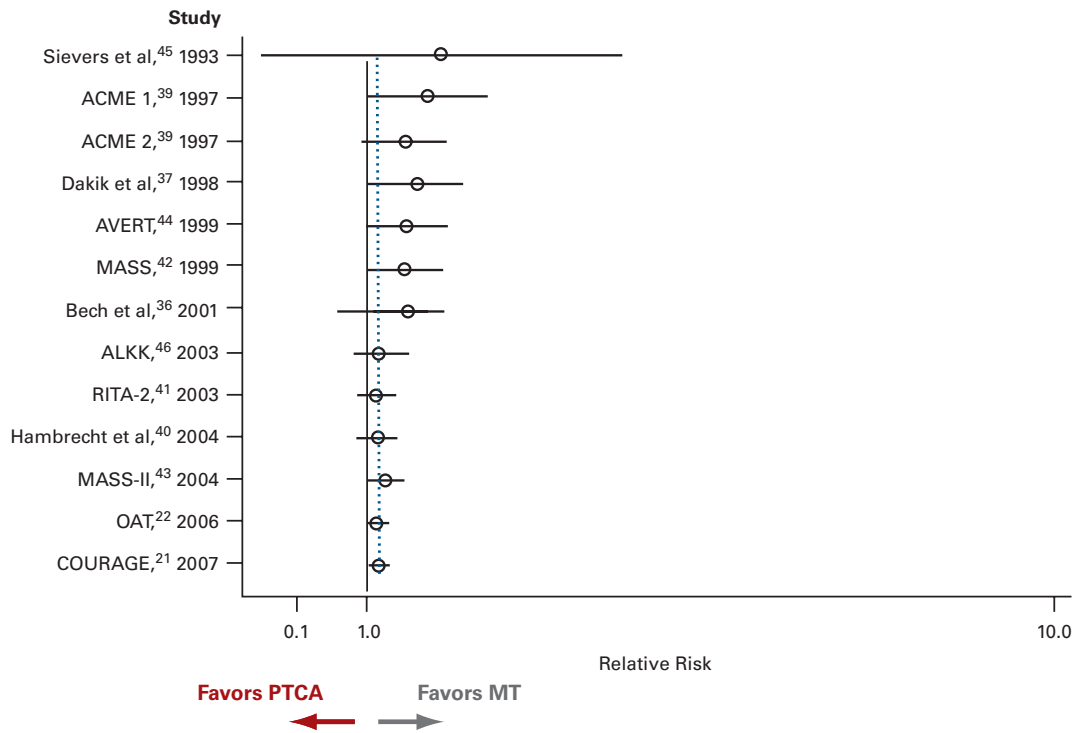
CI indicates confidence interval.

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



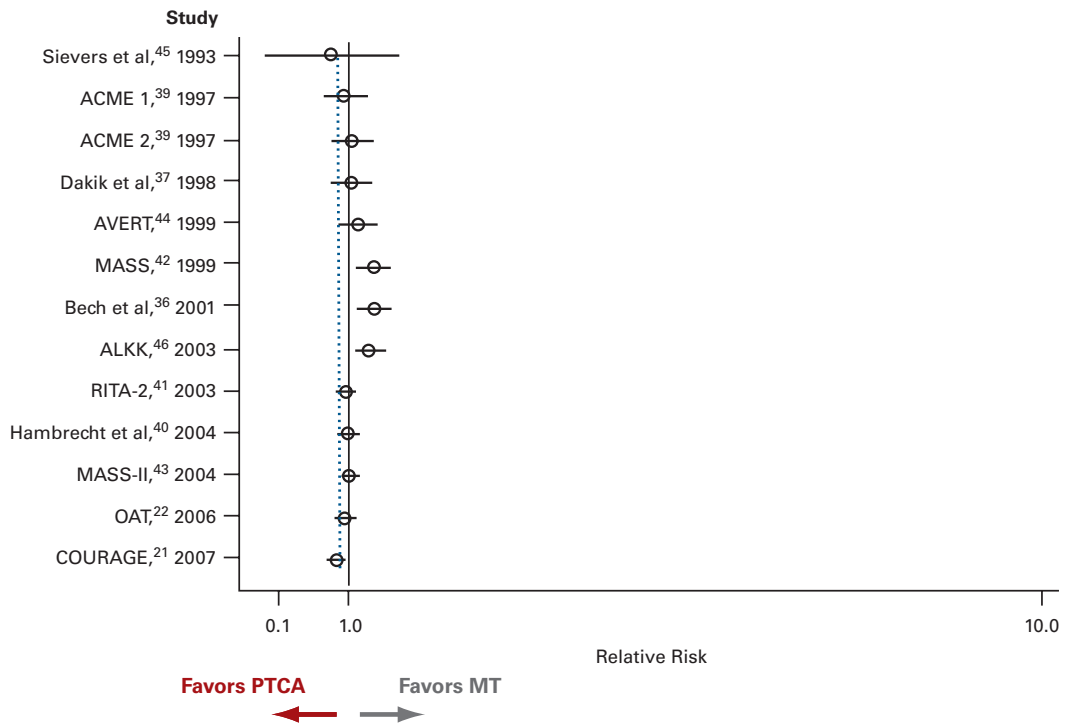
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

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



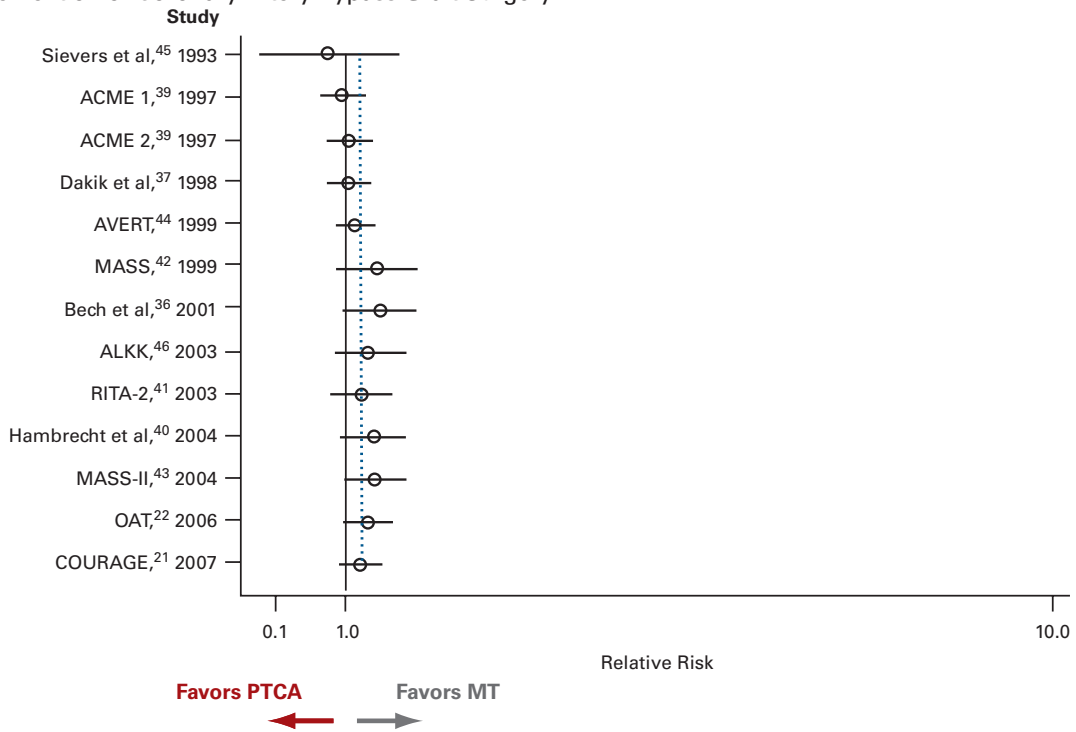
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

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



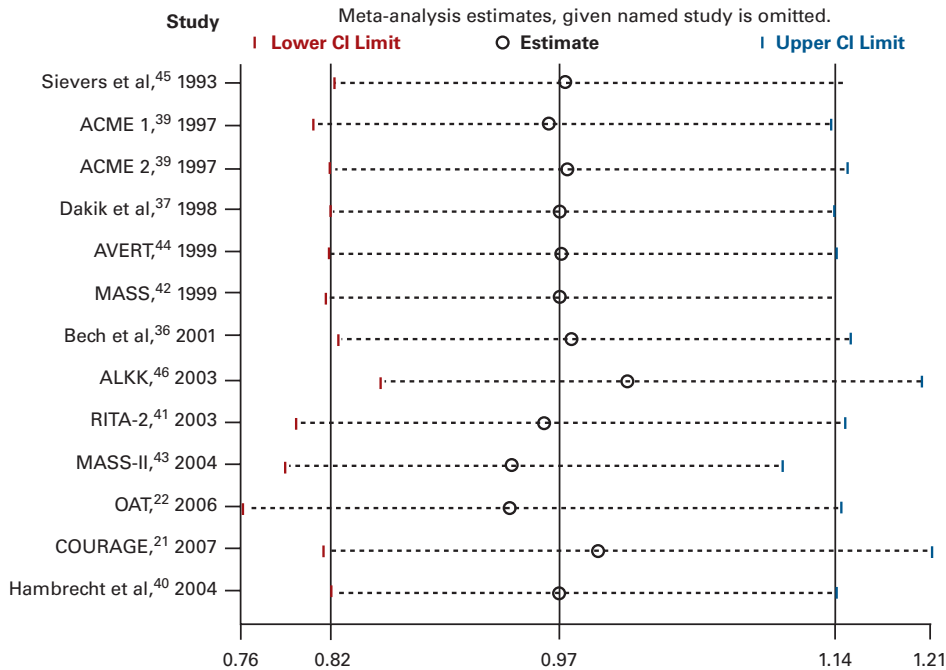
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

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



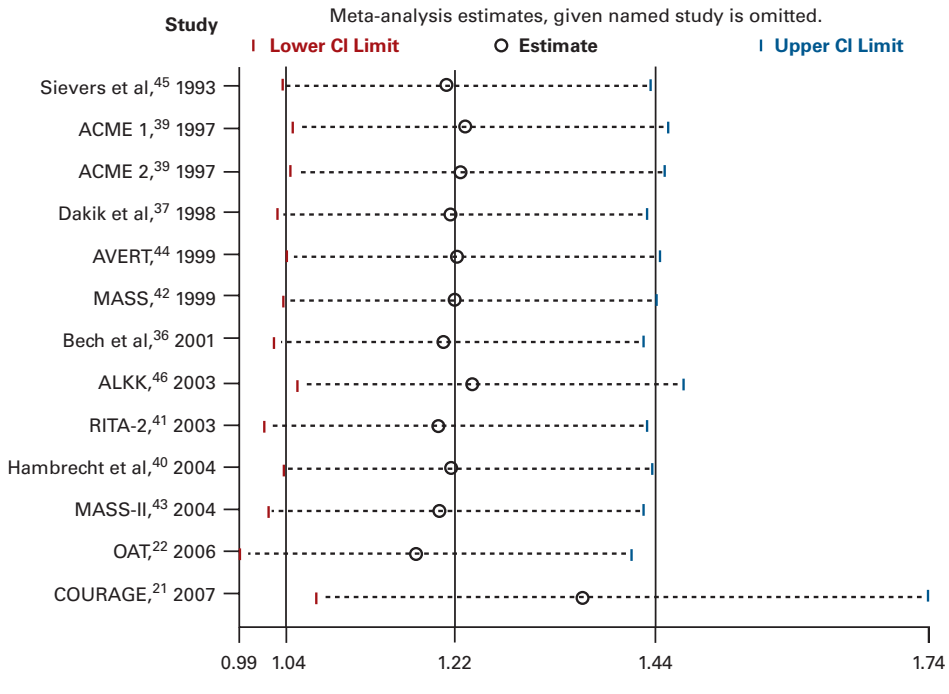
MT indicates medical therapy; PTCA, percutaneous transluminal coronary angioplasty.

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

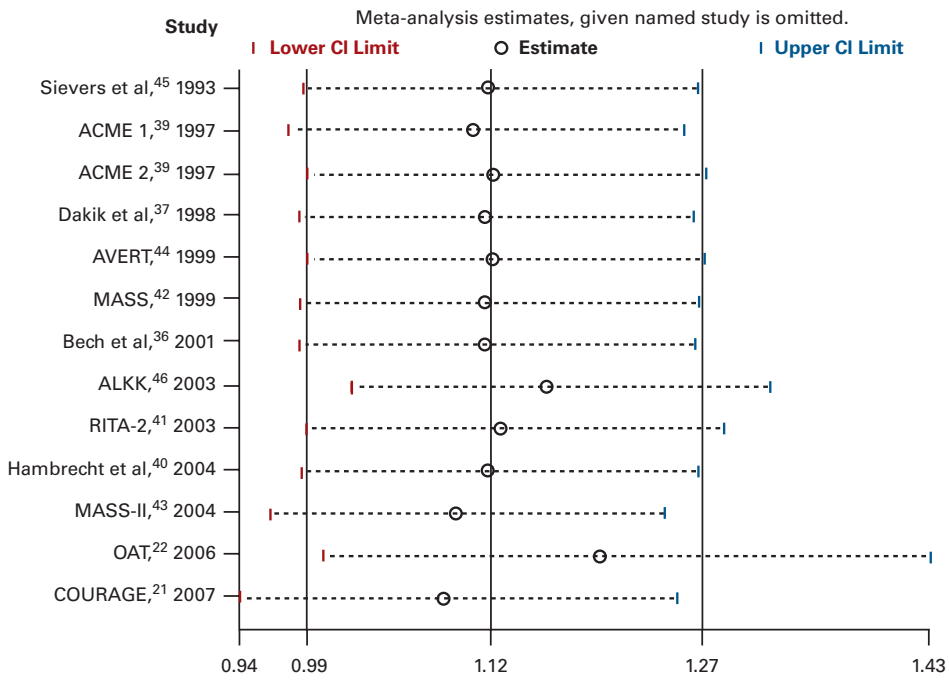


CI indicates confidence interval.

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

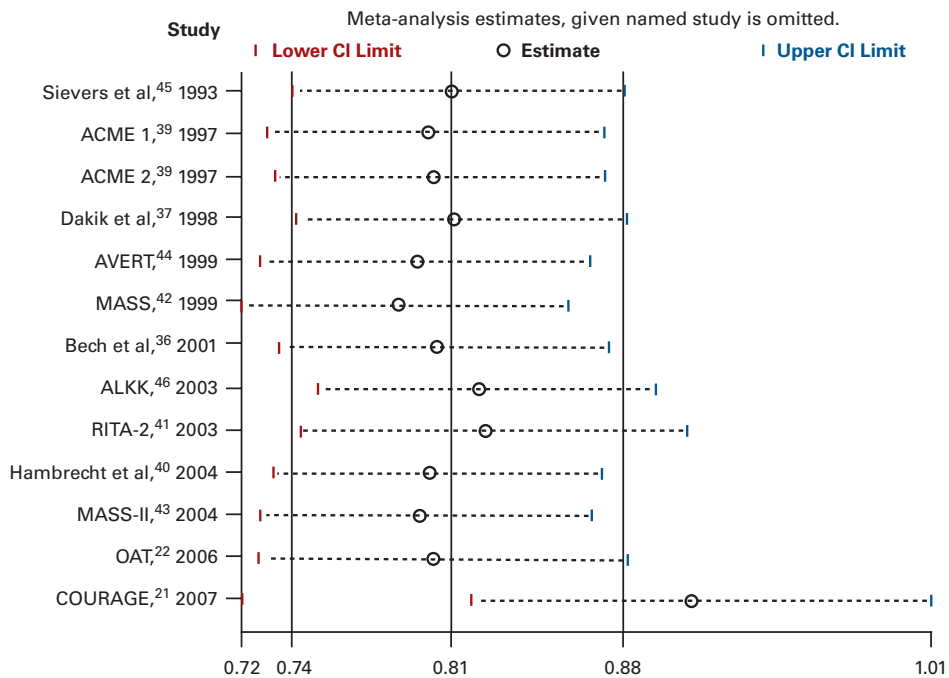


■ **eAppendix Figure 8.** Influence Analysis for Cardiac Death or Myocardial Infarction (Fixed Effects)



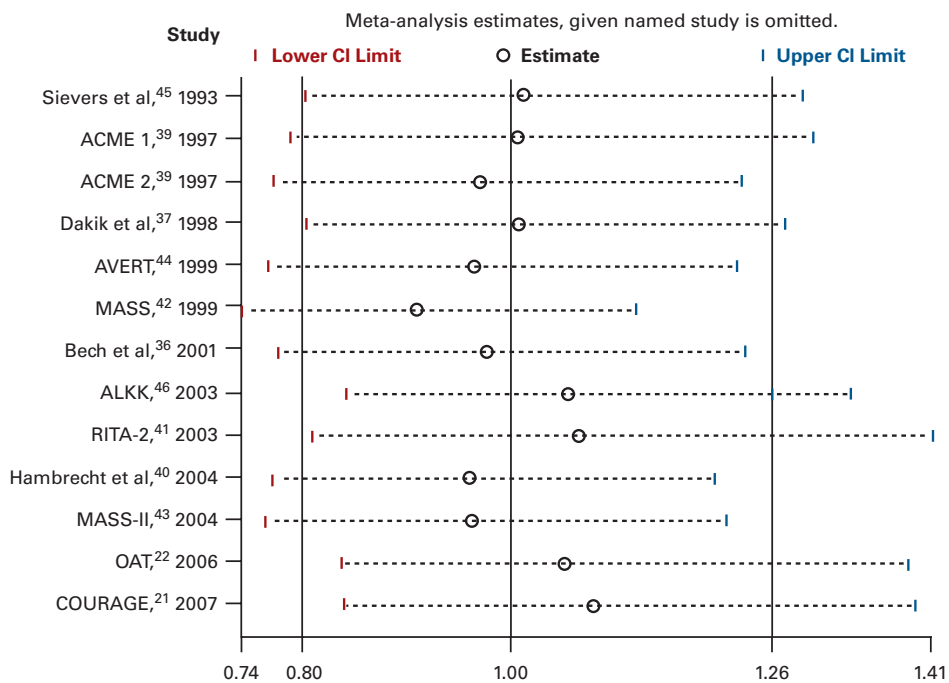
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■ eAppendix Figure 9. Influence Analysis for Follow-up Percutaneous Coronary Intervention or Percutaneous Transluminal Coronary Angioplasty (Fixed Effects)



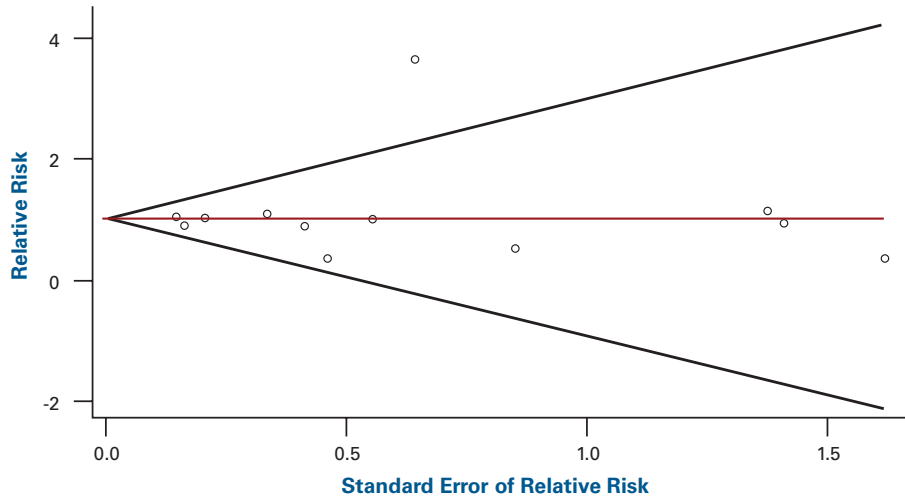
CI indicates confidence interval.

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

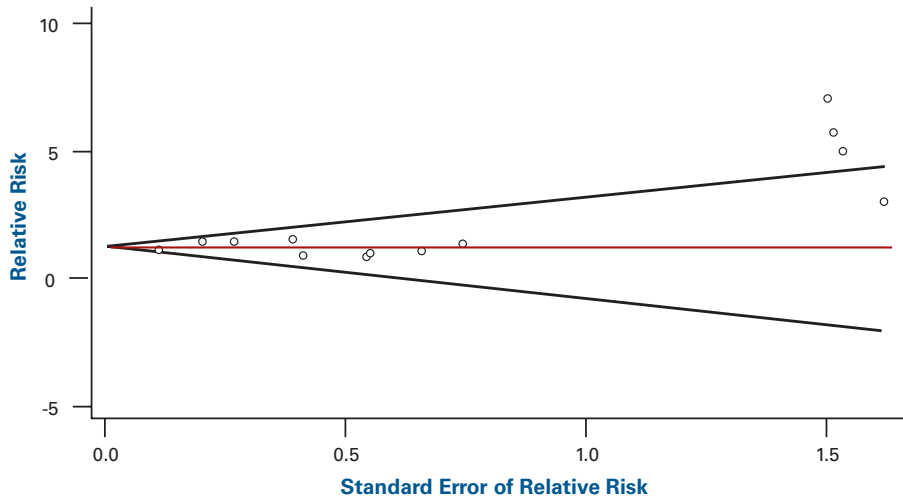


CI indicates confidence interval.

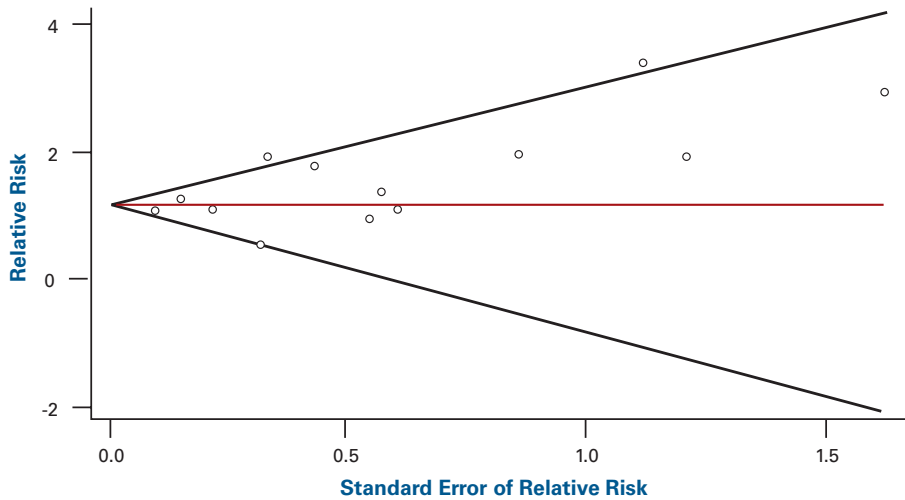
■ eAppendix Figure 11. Begg Funnel Plot With Pseudo 95% Confidence Limits for Death



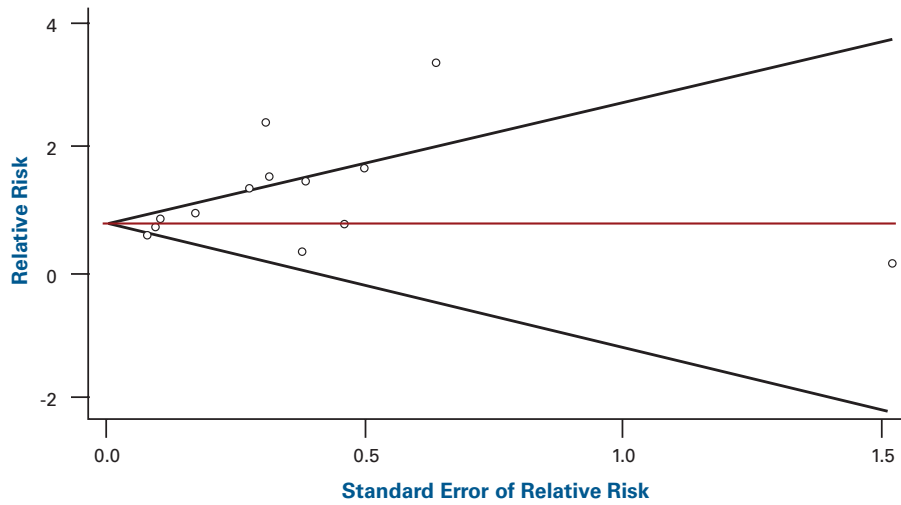
■ eAppendix Figure 12. Begg Funnel Plot With Pseudo 95% Confidence Limits for Nonfatal Myocardial Infarction



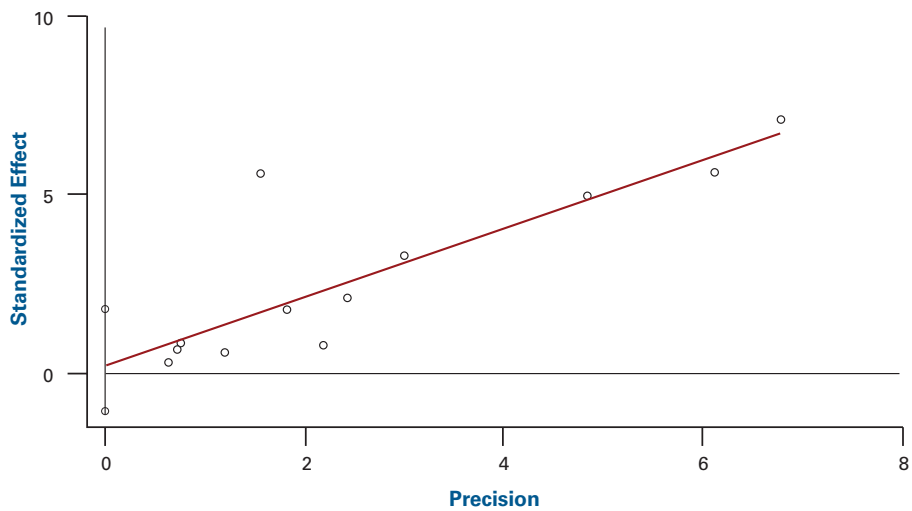
■ eAppendix Figure 13. Begg Funnel Plot With Pseudo 95% Confidence Limits for Cardiac Death or Myocardial Infarction



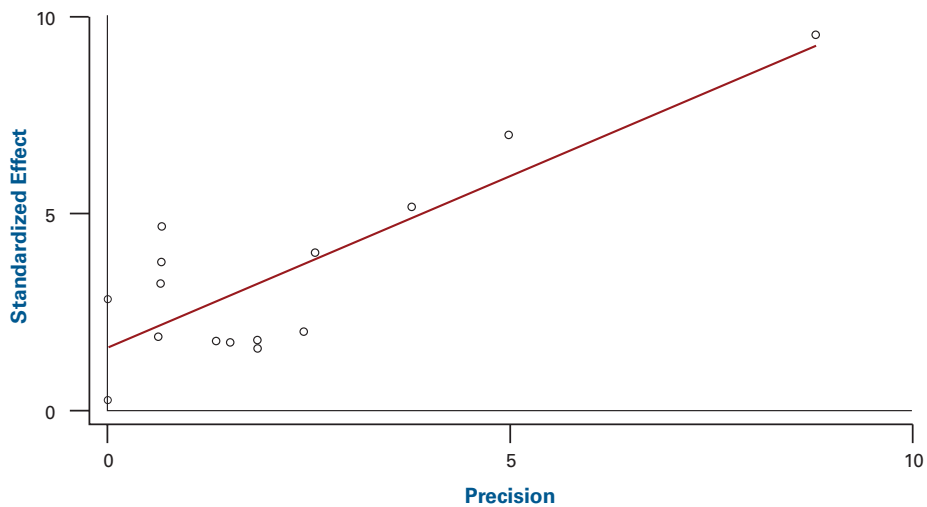
■ **eAppendix Figure 14.** Begg Funnel Plot for Follow-up Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery



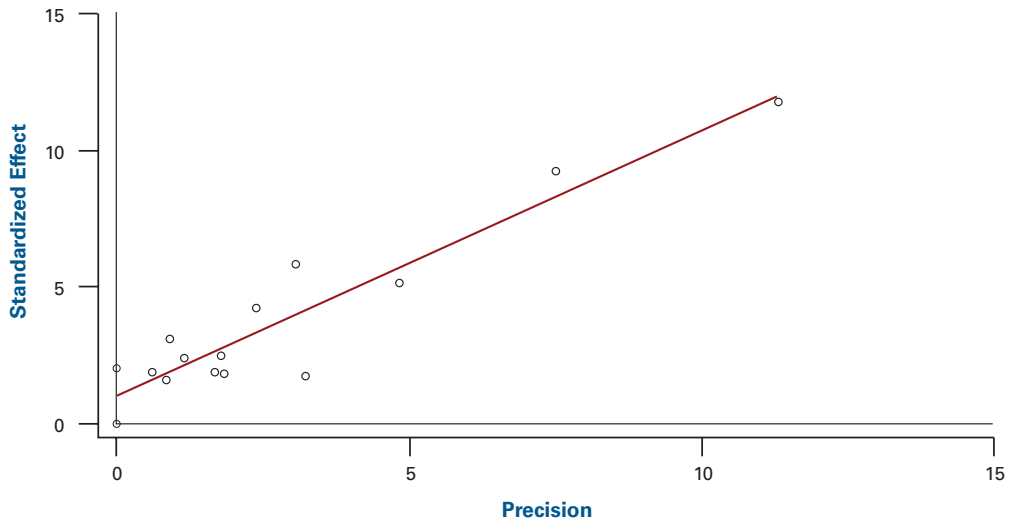
■ **eAppendix Figure 15.** Egger Publication Bias Plot for Death



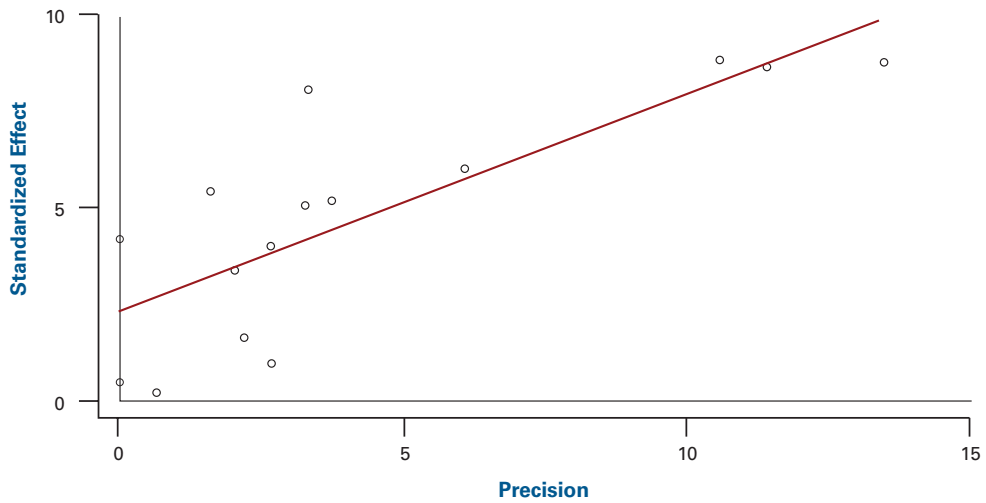
■ **eAppendix Figure 16.** Egger Publication Bias Plot for Nonfatal Myocardial Infarction



■ **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)

