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A Meta-Analysis of 17 Randomized Trials of a Percutaneous Coronary Intervention-Based Strategy in Patients With Stable Coronary Artery Disease

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Objectives This study assessed the impact on long-term mortality of percutaneous coronary intervention (PCI) versus medical treatment in patients with symptoms or signs of myocardial ischemia but no acute coronary syndrome.

Background The impact of PCI on the long-term prognosis of patients with stable coronary artery disease has not been established.

Methods We identified 17 randomized trials comparing a PCI-based invasive treatment strategy with medical treatment in 7,513 patients with symptoms or signs of myocardial ischemia but no acute coronary syndrome. Of these patients, 3,675 were assigned to the PCI group and 3,838 to the medical treatment group. The primary end point was all-cause death. The length of follow-up was in the range between 12 and 122 months, 51 months on average.

Results In the PCI group, 271 patients died compared with 335 patients in the medical treatment group, which corresponds to a 20% reduction in the odds ratio (OR) of all-cause death (OR: 0.80; 95% confidence interval [CI]: 0.64 to 0.99, p = 0.263 for heterogeneity across the trials). Allocation to the PCI group was associated with a nonsignificant 26% reduction in the OR of cardiac death (OR: 0.74, 95% CI: 0.51 to 1.06). In the PCI group, 319 patients had a nonfatal myocardial infarction after randomization compared with 357 patients in the medical treatment group (OR: 0.90, 95% CI: 0.66 to 1.23).

Conclusions These findings suggest that a PCI-based invasive strategy may improve long-term survival compared with a medical treatment-only strategy in patients with stable coronary artery disease. (J Am Coll Cardiol 2008;52:894–904) © 2008 by the American College of Cardiology Foundation

Coronary artery disease is the single largest killer of American men and women (1). In 2004 in the U.S., there were 840,000 cases discharged with the diagnosis of acute coronary syndrome, most of them with acute myocardial infarction (1). In the last decades, important advances have been made, which have provided patients with coronary artery disease with effective drugs able to improve significantly their prognosis, such as antiplatelet agents, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (2–4).

Percutaneous coronary interventions (PCIs) are increasingly being used in patients with various manifestations of coronary artery disease. They represent an established treatment strategy that improves survival and survival free of recurrent myocardial infarction in patients with ST-segment elevation myocardial infarction (5,6). Early invasive therapy also improves long-term survival and reduces late myocardial infarction in patients with non–ST-segment elevation acute coronary syndromes (7). Although PCI reduces symptoms in patients without acute coronary syndromes (8), its effects on the prognosis of these patients are still not defined. The assessment of this issue has been difficult for at least 2 reasons. First, patients with stable coronary artery disease have a very good prognosis and large sample size studies are required to assess potential differences in treatments regarding rare events (9,10). All studies performed to date were far from having sufficient power to assess mortality. Second, there is a certain risk associated with PCI, which leads to aggregation of events in a relatively short period after the procedure. Any potential beneficial effect of PCI compared with medical treatment alone may require time to offset this early

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excess risk, so that an extended follow-up may enable a more unbiased evaluation of the relative merits of these treatment strategies.

In an attempt to overcome these difficulties, 2 meta-analyses have been performed by pooling together the results from several randomized trials comparing invasive and medical treatment strategies in patients with no acute coronary syndromes (11,12). The first meta-analysis summarized the results of 6 trials including 1,904 patients, and the analysis of mortality was based on 26 death cases (11); the second meta-analysis summarized the results of 11 trials including 2,950 patients, and the analysis of mortality relied on 196 death cases (12). Even in a recent brief update, several randomized clinical trials with a design similar to those already included were left unaccounted for in the latter meta-analysis (13). This underscores the need for a new, comprehensive meta-analysis of all pertinent studies on the impact of PCI on the prognosis of patients with stable coronary artery disease.

The purpose of this meta-analysis was to evaluate whether PCI affects the long-term prognosis of patients with stable coronary artery disease.

Methods

Clinical trial selection. We intended to retrieve all randomized trials comparing a PCI-based invasive treatment strategy with a medical treatment strategy in patients with coronary artery disease and symptoms or signs of ischemia. Trials that included patients with acute coronary syndromes (with or without ST-segment elevation on electrocardiogram, with or without troponin or cardiac enzyme elevations) within the first week from presentation were excluded from this meta-analysis. The search was performed for the period between January 1, 1980, through August 20, 2007, and involved the PubMed database, U.S. National Institute of Health, Cochrane Central Register of Controlled Trials, proceedings of the American Heart Association, American College of Cardiology, and European Society of Cardiology, as well as internet-based sources of information on results of clinical trials in cardiology. Other data sources included reference lists of retrieved articles, and pertinent reviews and editorials from leading medical journals.

Nineteen randomized clinical trials were identified that assigned patients with no acute coronary syndromes to an invasive, PCI-based treatment strategy or medical-only treatment strategy (14–32). In 2 of these trials (22,31), neither symptoms nor signs of myocardial ischemia were a prerequisite for enrollment of patients in the study; thus, they were excluded from the present meta-analysis. Of the 17 trials included, 1 was published in abstract form (29) and 16 as full articles mostly presenting updated, extended follow-up (14–21,23–28,30,32). In 2 trials (23,30), patients were randomly assigned to 1 of 3 treatment groups: PCI, medical treatment, or coronary artery bypass grafting (CABG); for both of these trials, the CABG treatment arm was not included in this meta-analysis. However, patients who were randomly assigned to the PCI-based strategy or medical treatment group but received CABG were not excluded from this meta-analysis.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
OR = OR
PCI = percutaneous coronary intervention

Outcome variables. The primary end point of this meta-analysis was all-cause death within the longest follow-up period that was published by the investigators. Other outcomes of interest were death attributable to cardiac causes and myocardial infarction. The definition of the end point of myocardial infarction is shown in Table 1.

Statistical analysis. All trials included in this meta-analysis were prospective, randomized trials. The existence of an independent event committee was declared by the investigators of 12 of 17 trials (14–19,21,24–26,28,32). Baseline characteristics were evenly distributed between the 2 treatment groups in all trials. The actual treatment received was clearly shown for all trials. In all but 2 trials (16,27), the analysis was performed on the basis of the intention-to-treat principle. In the 2 trials that did not follow this principle, a total of 5 patients were excluded after randomization (16,27).

Treatment effect could not be assessed for trials in which the event of interest was not observed in any of the treatment groups. For trials in which only 1 of the treatment groups had no events of interest, the treatment effect estimate and its standard error were approximated from 2 × 2 contingency tables after adding 0.5 to each cell (33). We used the Cochran Q-test to assess heterogeneity across trials. Also, we calculated the I^2 statistic to measure the consistency between trials with values of 25%, 50%, and 75% defining the cutoff points for identifying low, moderate, and high degrees of heterogeneity, respectively (34). Treatment effects from individual trials were pooled using both the fixed effects Mantel-Haenszel model (35) and the random effects DerSimonian and Laird model (36). Several additional analyses were carried out to assess potential bias regarding the primary end point of the study. First, sensitivity analyses were performed by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Second, a funnel plot as well as the Egger test were used to assess publication bias (37). Third, a funnel plot was constructed to graphically illustrate the relationship between treatment effect size and sample size of the individual trials. Finally, we used a random-effects meta-regression analysis to estimate the extent to which other covariates—year of completion of patient enrollment, total sample size of the trial, proportion of patients with previous myocardial infarction, proportion of patients who received stents or CABG in the PCI group, proportion of patients who received non-protocol revascu-

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Table 1 Inclusion Criteria, Exclusion Criteria, and End Point Definitions of the Trials

Trial	Inclusion Criteria	Exclusion Criteria	Primary End Point	MI Definition
Sievers et al. (29)	Previous non–Q-wave MI; single-vessel disease of a major coronary artery, and no angina in daily life under medication	Previous Q-wave MI, positive stress test at 50 W, diabetes mellitus	NR	NR
ACME 1 (19)	Stable angina, markedly positive stress test, or MI within 3 months, stenosis >70% in the proximal 2/3 of a single vessel	Medically refractory unstable angina pectoris, previous PCI, left main artery stenosis >50%, >70% stenosis at more than 1 artery, EF <30%	Death, MI, recurrent hospitalization for cardiac disease, nonprotocol revascularization	New Q waves, hospital admission for chest pain with serum enzyme changes
ACME 2 (19)	Stable angina, markedly positive stress test, or MI within 3 months, stenosis >70% in the proximal 2/3 of 2 vessels	Medically refractory unstable angina pectoris, previous PCI, left main artery stenosis >50%, >70% stenosis at more than 2 arteries, EF <30%	Death, MI, recurrent hospitalization for cardiac disease, nonprotocol revascularization	New Q waves, hospital admission for chest pain with serum enzyme changes
ACIP (17)	Stable patients either free of angina or with symptoms that could be well controlled by medical therapy, by stress test, at least 1 episode of asymptomatic ischemia during 24-h ECG; angiographically-documented coronary artery disease	Recent MI (within 4 weeks), unstable angina, CCS IV, NYHA functional class III or IV, PCI within 6 months, CABG within 3 months, left main artery stenosis >50%	Death, death or MI, hospitalization for a cardiac condition (including nonprotocol revascularization)	NR
Dakik et al. (16)	Stable survivors of MI, large total (>20%) and ischemic (>10%) LV perfusion defect size	Clinical instability, EF >35%, 3-vessel disease, <50% left main artery stenosis	Reduction of LV perfusion defect	Increase in creatinine kinase-MB with new ST-segment changes and/or chest pain
AVERT (28)	LDL >115 mg/dl, triglycerides <500 mg. MI or unstable angina but not within 14 days, CCS I, II angina or asymptomatic, stenosis >50% in 1 or 2 vessels	Age >80 yrs, MI or unstable angina pectoris within previous 2 weeks, triple-vessel disease, left main artery stenosis, EF <40%	Ischemic events (cardiac death, cardiac arrest, MI, cerebrovascular accident, nonprotocol revascularization, worsening angina requiring hospitalization)	NR
MASS (23)	Stable angina, normal EF, inducible ischemia; stenosis >80% before first diagonal branch <12 mm in length	Prior revascularization, Q-wave MI, LV dysfunction, total occluded or tortuous or calcified lesions, >50% stenosis of left main artery	Cardiac death, MI, refractory angina requiring hospitalization	New Q waves with creatinine kinase-MB enzyme increase >3 times its normal value
Bech et al. (14)	CCS I or higher class angina, no evidence of reversible ischemia (noninvasive testing previous 2 months either negative, inconclusive, or not performed), significant de novo stenosis >50% in a native coronary artery	Total occlusion, Q-wave MI or unstable angina, small target vessel <2.5 mm	All-cause death, MI, revascularization, procedure-related complication	New Q waves or increase of serum creatinine kinase levels to >2 times the normal limit
ALKK (32)	Stable patients 8 to 42 days after ST-segment elevation MI; CCS I, CCS II angina pectoris, significant stenosis or occlusion of native infarct-related artery	CCS III, IV angina, >70% stenosis in noninfarct vessels, indication for CABG	Survival free of reinfarction, (re)intervention, CABG, readmission for severe angina	NR
RITA 2 (21)	Stable or unstable angina leading to admission, last episode at least 7 days before enrollment, single or multivessel disease, stenosis in at least 1 artery, >50% stenosis in 2 projections or >70% stenosis in 1 projection	Left main artery disease, previous revascularization, recent (<7 days) acute coronary syndrome	All-cause death or MI	New Q waves or convincing clinical history associated with typical ECG changes and serum activities
TIME (27)	Age >75 yrs with chronic CCS II angina or higher, chest pain refractory to at least 2 antianginal drugs	Acute MI within previous 10 days	Quality of life, major adverse cardiac events (death, MI, acute coronary syndrome)	Clinical event with significant ECG and enzyme changes
Hambrecht et al. (20)	CCS I to III angina with documented ischemia during stress test, 1 native coronary artery stenosis >75%	Age >70 yrs, acute coronary syndrome, recent MI (<2 months), EF <40%, revascularization within past 12 months, left main artery stenosis >25% or high-grade stenosis of left anterior descending artery	Angina-free exercise capacity, a composite of cardiac death, MI, stroke, revascularization, worsening angina with resulting hospitalization	NR

Continued on next page

Table 1 Continued

Trial	Inclusion Criteria	Exclusion Criteria	Primary End Point	MI Definition
DANAMI (24)	Inducible post-infarct ischemia, ability to perform a symptom-limited bicycle exercise	Drug-resistant angina pectoris, previous revascularization procedure	Death, reinfarction, admission with unstable angina, and combination	New Q waves in at least 2 ECG leads
INSPIRE (25)	Stable survivors of MI, total perfusion defect size >20%, ischemic defect size >10% (by adenosine SPECT), EF >35%	Cardiogenic shock, recurrent chest pain, acute coronary syndrome with primary PCI, NYHA functional class III and IV	Reduction of LV perfusion defect	NR
MASS II (30)	Documented ischemia (stress testing or CCS II or III angina), proximal multivessel coronary stenosis >70%	Age >80 yrs, unstable angina, acute MI, EF <40%, previous revascularization, single-vessel disease, left main artery stenosis >50%	Overall mortality, Q-wave MI, refractory angina requiring revascularization	New Q waves, symptoms compatible with MI associated with creatine kinase-MB >3 times the upper limit
SWISSI II (18)	First MI within preceding 3 months, no chest pain at maximal symptom-limited exercise test, sign of silent ischemia (confirmed by stress imaging), 1- or 2-vessel disease	NR	Survival free of major adverse cardiac events (cardiac death, MI, symptom-driven revascularization)	Typical chest pain, ST-segment elevation, typical increase of cardiac enzymes
COURAGE (15)	CCS I, CCS II angina, or initial CCS IV angina stabilized medically, stable post-MI, objective evidence of ischemia, stenosis >70% in at least 1 proximal coronary artery, and objective evidence of ischemia or at least 1 stenosis >80% and classic angina without provocative testing	Age >69 yrs, persistent CCS IV angina, markedly positive stress test, refractory heart failure or cardiogenic shock, EF <30%, revascularization within 6 months, unprotected left main artery stenosis >50%	Composite of death from any cause or MI	Acute coronary syndrome with new Q waves or positive cardiac markers

ACIP = Asymptomatic Cardiac Ischemia Pilot study; ACME = Angioplasty Compared to Medicine study; ALKK = Study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT = Atorvastatin versus Revascularization Treatment study; CABG = coronary artery bypass surgery; CCS = Canadian Cardiovascular Society; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation study; DANAMI = Danish Multicenter Randomized Study of Invasive Versus Conservative Treatment in Patients With Inducible Ischemia After Thrombolysis in Acute Myocardial Infarction study; ECG = electrocardiogram; EF = ejection fraction; INSPIRE = Adenosine Sestamibi Post-Infarction Evaluation study; LV = left ventricular; MASS = Medicine, Angioplasty, or Surgery Study; MI = myocardial infarction; NR = not reported; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RITA 2 = Second randomized Intervention Treatment of Angina study; SWISSI II = Swiss Interventional Study on Silent Ischemia Type II; TIME = Randomized Trial of Invasive Versus Medical Therapy in Elderly Patients.

larization in the medical treatment group—might have influenced the treatment effect. All p values are 2-sided. Statistical significance was assumed for $p < 0.05$. Statistical analysis was performed using the Stata software, version 9.2 (Stata Corp., College Station, Texas).

Results

Table 1 shows inclusion and exclusion criteria as well as the primary end point in individual trials. A total of 17 randomized trials including 7,513 patients were analyzed. Table 2 shows the main characteristics of the patients in each trial. Overall, the average age of the patients was 60 years, 18% of them were women, 54% had incurred myocardial infarction, and the average length of follow-up was 51 months. Ninety-two percent of the patients in the PCI-based strategy group received revascularization (43% balloon angioplasty, 41% stents, and 8% CABG). Drug-eluting stents were only used in 31 patients in 1 trial (15). In the medical treatment group, 28% of the patients received nonprotocol revascularization early or at some point in time during follow-up.

In the PCI group, 271 patients died, compared with 335 patients in the medical treatment group. Allocation to the PCI group was associated with a 20% reduction in the odds ratio (OR) of all-cause death (Fig. 1). There was no inconsistency across the trials (I^2 = 17%). The sensitivity analysis yielded ORs that ranged from 0.76 (95% confidence interval [CI]: 0.60 to 0.96) to 0.86 (95% CI: 0.72 to 1.03) that were not significantly different from the overall OR ($p \geq 0.591$). Figure 2A shows the funnel plot of publication bias, which was not statistically significant ($p = 0.261$) on the basis of the Egger test. Figure 2B shows that there was no relationship between sample size and treatment effect size. None of the covariates—year of completion of patient enrollment ($p = 0.982$), total sample size of the trial ($p = 0.634$), proportion of patients with previous myocardial infarction ($p = 0.119$), proportion of patients in the PCI group who received stents ($p = 0.9361$) or CABG ($p = 0.392$), and proportion of patients in the medical treatment group who received nonprotocol revascularization ($p = 0.652$)—showed a significant interaction with treatment effect.

A separate analysis was performed to investigate the role of length of follow-up. We assessed all-cause death after follow-up periods of up to 1 year, 3 years, and 5 years, and added these data to our overall analysis, encompassing a follow-up period of up to 10 years. For this purpose, we sought additional information on earlier mortality in the trials from initial publications (38–42) or directly from investigators (18). Figure 3 shows the relationship between the length of follow-up and the ORs of all-cause death associated with PCI versus medical treatment.

Table 2 Main Characteristics of the Trials

Trial	Year of Most Recent Publication	Enrollment Period	Total No. of Patients	Mean Age (yrs)	Women (%)	Previous MI (%)	Protocol Revascularizations in PCI Group (%) Total (CABG)	Use of Stents in PCI Group (%)	Nonprotocol Revascularizations in Medical Group (%) Total (CABG)	Length of Follow-Up (Months)
Sievers et al. (29)	1993	NR	88	56	NR	55	100 (0)	0	20 (5)	24
ACME 1 (19)	1997	1987–1990	227	60	0	34	96 (0)	0	41 (11)	60
ACME 2 (19)	1997	1987–1990	101	60	0	45	100 (0)	0	40 (30)	60
ACIP (17)	1997	1991–1993	558	62	14	40	89 (41)	0	29 (22)	24
Dakik et al. (16)	1998	1995–1996	44	54	41	100	100 (0)	29	9 (9)	12
AVERT (28)	1999	1995–1996	341	58	16	42	94 (0)	28	12 (1)	20
MASS (23)	1999	1988–1991	144	65	42	0	100 (0)	0	17 (11)	60
Bech et al. (14)	2001	NR	181	61	36	25	100 (0)	46	7 (0)	24
ALKK (32)	2003	1994–1997	300	57	13	100	93 (0)	16	24 (NR)	52
RITA 2 (21)	2003	1992–1996	1,018	58	18	47	93 (0)	8	35 (12)	84
TIME (27)	2004	1996–2000	301	80	42	47	71 (20)	44	42 (NR)	48
Hambrecht et al. (20)	2004	1997–2001	101	60	0	46	100 (0)	100	6 (0)	12
DANAMI (24)	2006	1990–1994	1,008	57	18	100	82 (29)	0	20 (NR)	28
INSPIRE (25)	2006	1999–2002	205	64	24	100	67 (26)	39	26 (10)	60
MASS II (30)	2006	1995–2000	408	60	32	46	95 (0)	68	24 (15)	60
SWISSI II (18)	2007	1991–1997	201	55	12	100	100 (0)	0	44 (NR)	122
COURAGE (15)	2007	1991–2004	2,287	61	15	38	96 (0)	90	31 (7)	54

Abbreviations as in Table 1.

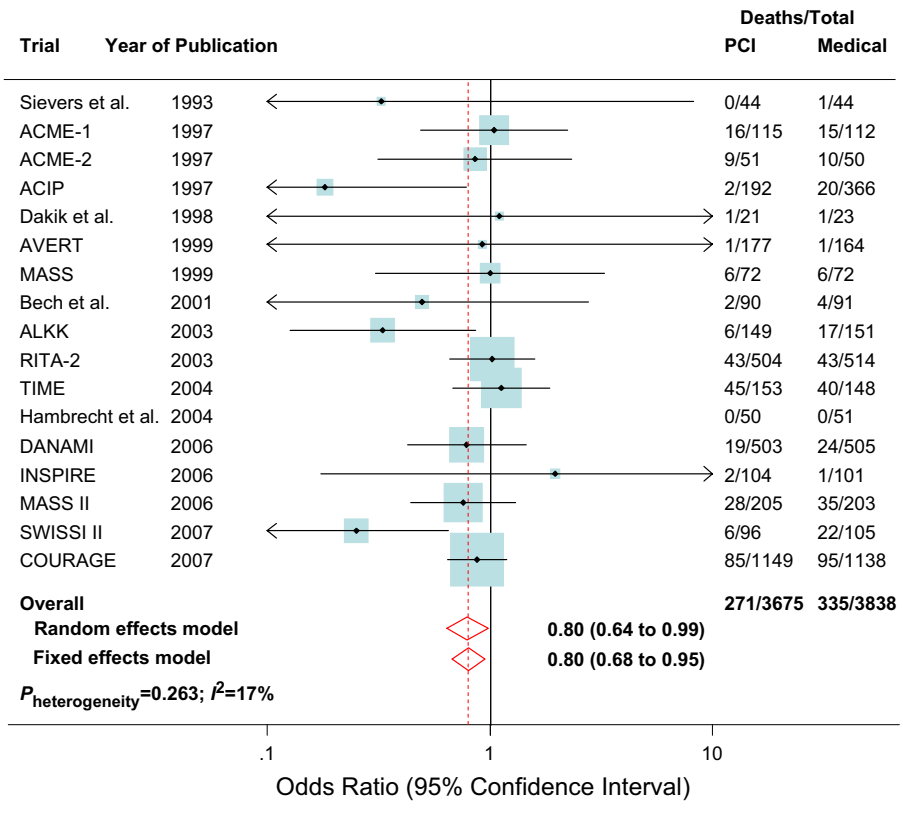

Figure 1 Odds Ratios for Mortality in Individual Trials Comparing the PCI-Based Strategy With Medical Treatment Strategy

Pooled odds ratios are also shown. PCI = percutaneous coronary intervention.

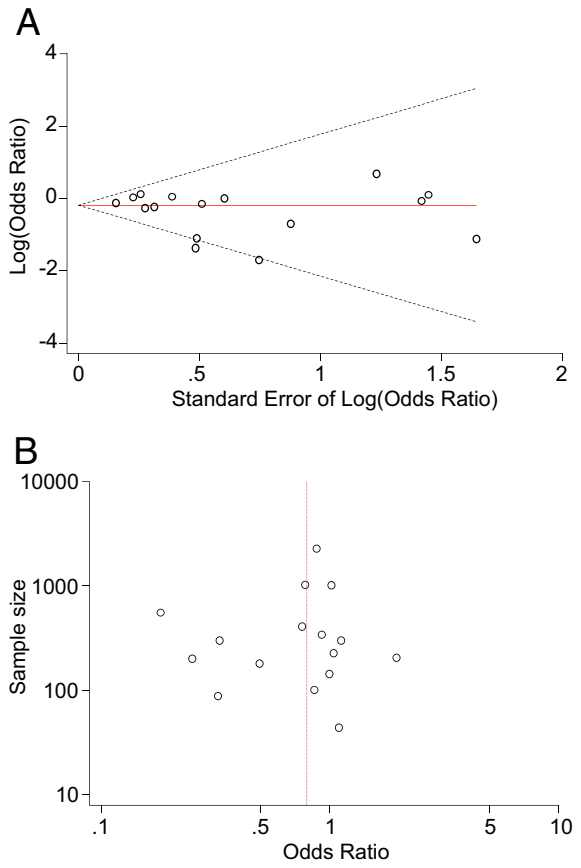

Figure 2 **Assessment of Publication Bias and Relationship Between Sample Size of the Trial and Treatment Effect**

(A) Funnel plot for assessment of publication bias of trials comparing the PCI-based strategy with medical treatment strategy regarding mortality. The **circles** correspond to the treatment effects from individual trials, the **red line** shows the summary estimate, and the **diagonal lines** show the expected 95% confidence intervals around the summary estimate. Note that there is no evident asymmetry of the points in relation to the summary estimate that might indicate a relevant publication bias. **(B)** Relationship between sample size of the trial and treatment effect regarding mortality. Both treatment effect and sample size are shown on a logarithmic scale. Note the lack of an evident relationship between sample size and observed treatment effect. PCI = percutaneous coronary intervention.

Patients with acute coronary syndromes were excluded from the studies included in this meta-analysis. However, all but 1 trial (23) had included patients with previous myocardial infarction in a proportion ranging from 25% to 100%. In 4 of the 5 trials that included only patients with previous myocardial infarction (16,24,25,32), myocardial infarction was recent (<4 weeks) according to current guidelines (43). In the remaining trial (18), the time interval from myocardial infarction was on average >8 weeks. When calculation regarding all-cause death was confined to the 4 trials enrolling patients with recent myocardial infarction, PCI was associated with an OR of 0.65 (95% CI: 0.37 to 1.12) from the random effects model and 0.64 (95% CI: 0.40 to 1.05) from the fixed effects model. When calculation was confined to the remaining 13 trials, PCI was associated with an OR of 0.83 (95% CI: 0.65 to 1.04) from the random effects model and 0.83 (95% CI: 0.69 to 1.00) from the fixed effects model. These results are shown in Figure 4. Figure 4 also shows the results of 2 additional subset analyses regarding treatment effect on mortality. The superiority of PCI was confined to the 14 trials in which coronary angiography was required before randomization (14–21,23,26,28–30,32). In addition, the exclusion of the 4 trials in which CABG was allowed as a treatment option in the PCI-based group (17,24,25,27) did not make any difference in treatment effect regarding all-cause mortality: PCI was associated with an OR of 0.80 (95% CI: 0.64 to 0.99) from the random effects model and 0.80 (95% CI: 0.66 to 0.97) from the fixed effects model.

The cardiac cause of death was reported in 13 trials (14–16,18,20,21,23,25,27–29,32,44). In the PCI group, 115 patients died of cardiac causes compared with 151 patients in the medical treatment group. Allocation to the PCI group was associated with a 26% reduction in the OR of cardiac death (Fig. 5). There was a slight inconsistency across the trials (I^2 = 29%). For the same trials, we calculated the ORs for noncardiac death. A PCI was associated with an OR of 0.96 (95% CI: 0.67 to 1.36) from the random effects model and 0.95 (95% CI: 0.73 to 1.24) from the fixed effects model.

In the PCI group, 319 patients had nonfatal myocardial infarction after randomization compared with 357 patients in the medical treatment group. Allocation to the PCI group was associated with a slight and nonsignificant 10% reduction in the OR of nonfatal myocardial infarction (Fig.

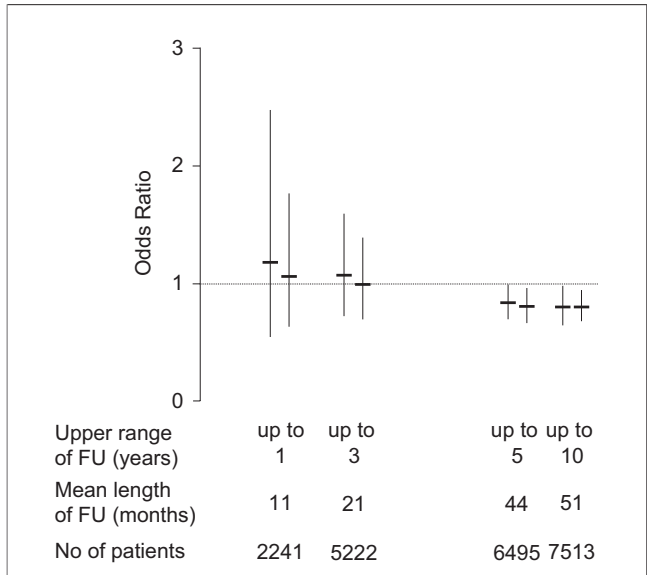

Figure 3 **Follow-Up Interval and Odds Ratios for Mortality for PCI Versus Medical Treatment**

Odds ratios are shown in pairs, from the random effects model on the left and from the fixed effects model on the right. FU = follow-up; PCI = percutaneous coronary intervention.

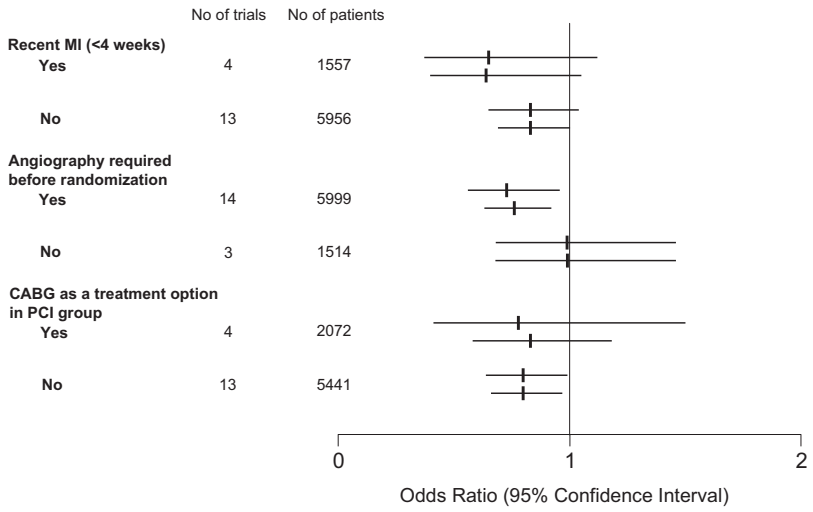

Figure 4 Odds Ratios for Mortality for PCI Versus Medical Treatment in Various Subsets

Odds ratios are shown in pairs, from the random effects **(upper line)** and from the fixed effects model **(lower line)**.
CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention.

6). However, there was a moderate inconsistency of treatment effects across the trials (I^2 = 56%). A significant interaction with treatment effect regarding nonfatal myocardial infarction was observed for the proportion of patients with previous myocardial infarction (p = 0.004: the higher the proportion, the lower the OR reduction by PCI vs. medical treatment). None of the other covariates—year of completion of patient enrollment (p = 0.923), total

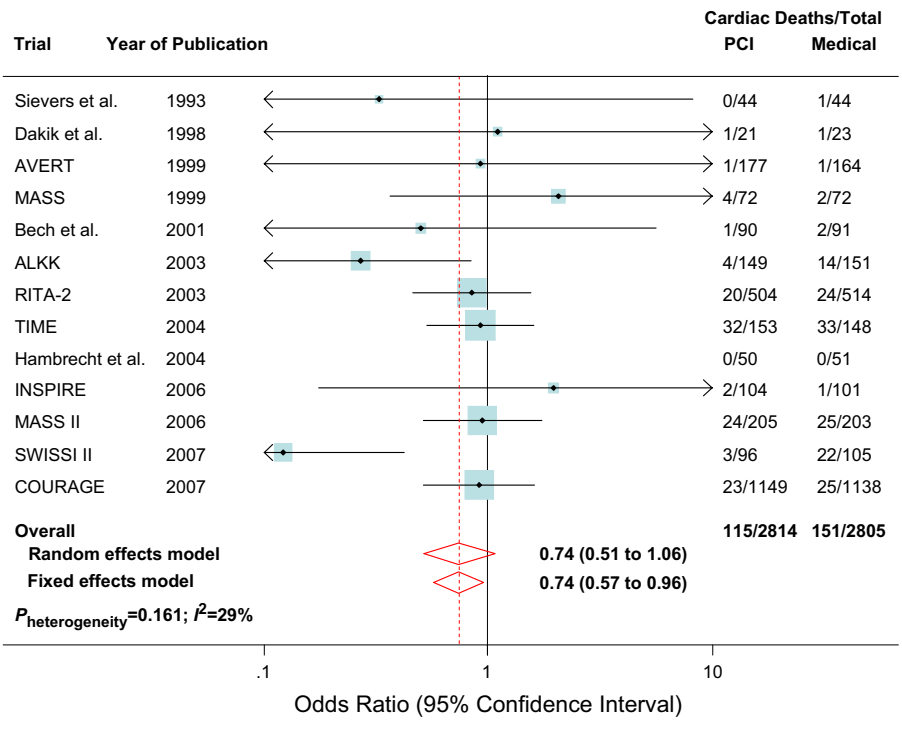

Figure 5 Odds Ratios for Cardiac Death in Individual Trials Comparing the PCI-Based Strategy With Medical Treatment Strategy

Pooled odds ratios are also shown. PCI = percutaneous coronary intervention.

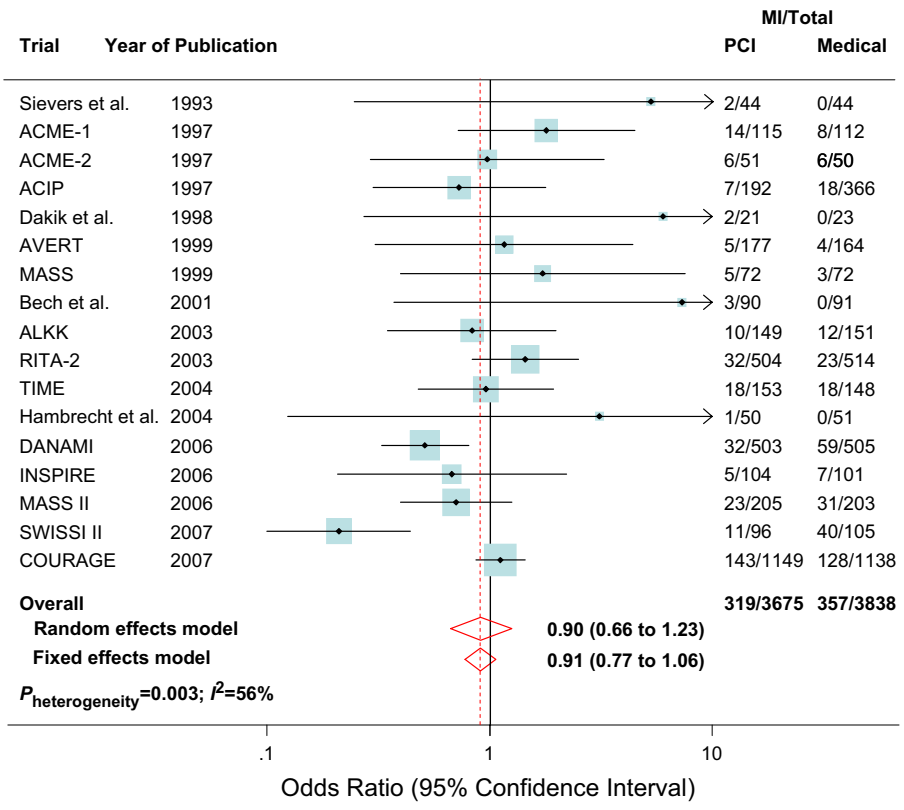

Figure 6 **Odds Ratios for Nonfatal Myocardial Infarction in Individual Trials Comparing the PCI-Based Strategy With Medical Treatment Strategy**

Pooled odds ratios are also shown. MI = nonfatal myocardial infarction; PCI = percutaneous coronary intervention.

sample size of the trial (p = 0.497), proportion of patients in the PCI group who received stents (p = 0.596) or CABG (p = 0.362), and proportion of patients in the medical treatment group who received nonprotocol revascularization (p = 0.183)—showed a significant interaction with treatment effect. We also calculated the ORs for the composite of all-cause death or nonfatal myocardial infarction. A PCI was associated with an OR of 0.80 (95% CI: 0.60 to 1.05) from the random effects model and 0.84 (95% CI: 0.74 to 0.96) from the fixed effects model.

Discussion

We pooled together the results from 17 randomized trials on the value of a PCI-based treatment strategy in 7,513 patients with stable coronary artery disease. Treatment effect size was calculated from both random and fixed effects models, knowing that the former is more appropriate in case of significant heterogeneity across trials but may inflate the importance of small randomized studies. The primary analysis focused on mortality within an average follow-up period of 51 months. The analysis of the 606 death cases observed in the entire population showed that a PCI-based treatment strategy is associated with a 20% reduction in the OR of death when compared with a medical treatment-only strategy.

The effect size was not statistically dependent on any specific trial characteristics, including sample size and length of follow-up. However, it seemed to be greater among in-patients with a recent (<4 weeks) myocardial infarction, in whom there was an approximate 35% reduction in the odds of death with PCI compared with patients without recent myocardial infarction, in whom the odds of death with PCI was reduced by approximately 17%. In fact, even in a subset analysis of a recent trial, PCI was more effective than medical therapy at relieving ischemia, and rates of death and myocardial infarction were reduced in patients with absent or minimal ischemia (45). It is important to note that the included randomized trials, and consequently the entire present meta-analysis, should not be considered as a head-to-head comparison of 2 mutually exclusive treatment strategies. On the contrary, all of them evaluated the value of the PCI-based strategy as an addition to medical therapy, because patients in both study arms received medical treatment. Furthermore, 28% of the patients assigned to medical treatment only did receive revascularization at some point in time during follow-up. This

might have blunted differences in survival between the 2 treatment groups in a way that cannot be predicted. Finally, individual patient data were not available for this study, which precluded several subgroup analyses. In particular, we were not able to assess the influence of the severity of ischemia at baseline on the potential benefit with PCI.

Another aspect that should be considered is that enrollment of patients was extended over a 17-year period, time in which major developments have been recorded in both the pharmacological and the interventional treatment of coronary artery disease. In fact, the year of completion of patient enrollment did not have a significant impact on the overall result as shown by the meta-regression analysis. Obviously, patients of both study arms have benefited from advances in drug therapy. Bare-metal stents were used in less than one-half of the patients included in the present meta-analysis, and drug-eluting stents were implanted in an irrelevant number of patients. Although no advantage in survival has been attributed to both bare-metal and drug-eluting stents (46,47), this does not exclude that future advances in both pharmacological and interventional treatment of patients with coronary artery disease may reduce or further accentuate the difference in mortality observed in this meta-analysis.

Well-defined inclusion criteria relevant to the question to be addressed and a comprehensive accounting for all studies meeting those criteria are crucial to the success of the meta-analysis. The present meta-analysis intended to include all studies that investigated the relative merits of PCI in patients with stable coronary artery disease and symptoms or signs of ischemia. Two randomized trials have evaluated the role of PCI patients with persistent occluded infarct-related vessels after myocardial infarction, mostly without any clues of ischemia (22,31). In essence, this was done with the objective of assessing the open artery hypothesis. The present meta-analysis did not include the latter 2 trials because of the absence of an ischemia criterion. The same was done by Katritsis and Ioannidis in their initial (12) and updated (13) version of the meta-analysis. On the other side, we included all 4 trials that enrolled stable post-recent infarct patients with symptoms or signs of ischemia (16,24,25,32). Only 3 of these trials (16,25,32) were included in the meta-analysis by Katritsis and Ioannidis (13). We included all 4 trials that used CABG instead of PCI in 20% to 41% of the patients in the PCI-based strategy group (17,24,25,27). In these trials, the form of invasive treatment therapy was selected after randomization, and their exclusion from our meta-analysis would have violated the intention-to-treat principle. Katritsis and Ioannidis (13) included only 1 of these studies (25) in their meta-analysis. Thus, the present study constitutes a consistent and comprehensive investigation of available evidence by meta-analytical methods.

There is little doubt that PCI relieves ischemia and improves the exercise capacity of patients with angina pectoris (48). The results of this meta-analysis add significantly to the value of the PCI-based strategy because they contain the novel finding of a substantial reduction of long-term mortality by the use of this strategy. A reduction of similar magnitude (20%) in patients with stable coronary artery disease has not been a frequent finding of clinical trials in the past. Meta-analyses pooling the results of randomized trials on secondary prevention in patients with coronary artery disease have shown a reduction of all-cause death of 16% with statins (49) and 23% with beta-blockers (50). Nevertheless, the marginal significance level achieved in the present analysis of mortality may still require the performance of a large mortality trial to confirm the potential superiority of the PCI strategy in patients with stable coronary artery disease.

A PCI of significant coronary artery stenoses may reduce the risk of death by improving regional blood flow and stabilizing the underlying plaque through neointima formation that occurs after arterial wall injury. The risk of cardiac death was also reduced in our pooled analysis of the 13 trials that reported this event, although the lack of the information in 4 trials might have reduced the significance of this finding. The risk of nonfatal myocardial infarction was only slightly decreased. Interestingly, more recent trials showed a greater reduction in the risk of nonfatal myocardial infarction, probably because of improvements in the PCI technology and experience as well as in adjunct antithrombotic therapy. Whereas there was consistency across trials in the treatment effect size regarding all-cause mortality, there was a slight inconsistency with respect to cardiac death and a moderate inconsistency regarding myocardial infarction. This is a new clue of both the difficulties arising from pooling together results that partly depend on event definition and the robustness of all-cause mortality as an end point in the evaluation of treatment strategies. However, although the slight decrease in the risk of nonfatal myocardial infarction should not be overstated, even the lack of an increased risk of this adverse event in the PCI group may be considered a positive finding when combined with the reduced overall mortality observed with this strategy. Apparently, the PCI-based strategy is associated with a reduced risk of large myocardial infarctions leading to cardiac death, and, at least no increase in the long-term risk of smaller, nonfatal myocardial infarctions despite the known finding of myocardial injury that some patients incur early after the procedure.

Conclusions

These findings suggest that a PCI-based invasive strategy may improve long-term survival compared with a medical treatment-only strategy in patients with stable coronary artery disease. This justifies the performance of a new randomized clinical trial sufficiently powered for evaluating the impact of PCI on long-term mortality.

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