Percutaneous Coronary Intervention Versus Optimal Medical Therapy in Stable Coronary Artery Disease

A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background—The role of percutaneous coronary intervention (PCI) in the management of stable coronary artery disease remains controversial. Given advancements in medical therapies and stent technology over the last decade, we sought to evaluate whether PCI, when added to medical therapy, improves outcomes when compared with medical therapy alone.

Methods and Results—We performed a systematic review and meta-analysis, searching PubMed, EMBASE, and CENTRAL databases, until January 2012, for randomized clinical trials comparing revascularization with PCI to optimal medical therapy (OMT) in patients with stable coronary artery disease. The primary outcome was all-cause mortality, and secondary outcomes included cardiovascular death, nonfatal myocardial infarction, subsequent revascularization, and freedom from angina. Primary analyses were based on longest available follow-up with secondary analyses stratified by trial duration, with short-term (≤1 year), intermediate (1–5 years), and long-term (≥5 years) time points. We identified 12 randomized clinical trials enrolling 7182 participants who fulfilled our inclusion criteria. For the primary analyses, when compared with OMT, PCI was associated with no significant improvement in mortality (risk ratio [RR], 0.85; 95% CI, 0.71–1.01), cardiac death (RR, 0.71; 95% CI, 0.47–1.06), nonfatal myocardial infarction (RR, 0.93; 95% CI, 0.70–1.24), or repeat revascularization (RR, 0.93; 95% CI, 0.76–1.14), with consistent results over all follow-up time points. Sensitivity analysis restricted to studies in which there was >50% stent use showed attenuation in the effect size for all-cause mortality (RR, 0.93; 95% CI, 0.78–1.11) with PCI. However, for freedom from angina, there was a significant improved outcome with PCI, as compared with OMT (RR, 1.20; 95% CI, 1.06–1.37), evident at all of the follow-up time points.

Conclusions—In this most rigorous and comprehensive analysis in patients with stable coronary artery disease, PCI, as compared with OMT, did not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization. PCI, however, provided a greater angina relief compared with OMT alone, larger studies with sufficient power are required to prove this conclusively. **(*Circ Cardiovasc Interv.* 2012;5:476-490.)**

Key Words: angina ■ coronary artery disease ■ optimal medical therapy ■ percutaneous coronary intervention

Coronary artery disease (CAD) is the leading cause of death worldwide, contributing to over 7.2 million deaths annually.[1] Early revascularization has been well validated to show a reduction in cardiovascular events in the management of ST segment elevation myocardial infarction.[2–10] In addition, revascularization has been shown to improve cardiovascular outcomes in the management of non-ST segment elevation myocardial infarction and unstable angina.[11–14] However, the optimal treatment strategy of nonacute CAD, manifest clinically as stable angina, is not well defined. Current guidelines for the management of stable angina emphasize risk factor modification, namely smoking cessation, exercise, diabetes mellitus management, lipid lowering, antianginal, and antihypertensive therapies.[15] With advancements in medical therapies over the last 2 decades, it is unclear whether percutaneous coronary intervention (PCI) provides a prognostic advantage over optimal medical therapy (OMT) in the management of stable angina patients.

Recent trials including Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[16] and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)[17,18] have shown no

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significant difference in outcomes in the treatment of stable angina patients with revascularization versus OMT alone. Several reviews and meta-analyses have been conducted to determine the role of PCI in patients with stable CAD, with some suggesting a greater relief of angina symptoms (odds ratio, 1.69; 95% CI, 1.24-2.30),[19,20] and others showing no improvement in death, myocardial infarction (MI), or need for subsequent revascularization using the invasive strategy,[21] though an analysis in 2008 by Schömig et al,[22] incorporating data from the large Swiss Interventional Study on Silent Ischemia Type II (SWISS-II)[23] and COURAGE trials, suggested an improvement in all-cause mortality in the revascularized group (odds ratio, 0.80; 95% CI, 0.64–0.99). This analysis included trials in which the revascularization group combined patients undergoing PCI or coronary artery bypass grafting (CABG), and also included those without stable CAD (ie, those patients with a recent acute coronary syndrome).

The objective of this review was to determine whether revascularization with PCI reduces cardiovascular outcomes when compared with OMT in patients with stable CAD.

WHAT IS KNOWN

- The optimal management of stable coronary artery disease is controversial. With evolving percutaneous coronary intervention strategies and novel medical therapies, the best evidence-based treatment strategy is unknown.

WHAT THE STUDY ADDS

- In this meta-analysis of 7182 individuals, percutaneous coronary intervention, as compared with optimal medical therapy, did not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization.
- Revascularization with percutaneous coronary intervention was associated with greater angina relief, compared with optimal medical therapy alone.
- It is unknown whether the above results hold true in the contemporary era of third generation drug-eluting stents and contemporary medical management.
- Larger studies with sufficient power are required to detect contemporary differences in treatment strategies.

Methods

Eligibility Criteria

We conducted PubMed, EMBASE, and CENTRAL searches (until January 2012) using medical subject heading and keyword terms related to the diagnosis of stable CAD, the intervention of PCI, and comparison of medical therapy. No imposed language or date restrictions were applied. Our search strategy in PubMed incorporated the Cochrane Highly Sensitive Search Strategy for identification of randomized clinical trials.[24] The details of the search strategies are listed in the online-only Data Supplement Appendix. After identification of eligible articles for inclusion in the systematic review, we searched the Web of Science citation index to identify any potentially relevant articles that were cited by our included articles. We also searched the reference list of previously published meta-analyses[19–22] and the original articles identified for full text review to find other eligible trials.

Eligible trials fulfilled the following criteria: (1) cohort enrolled being stable CAD patients, CAD defined by coronary angiography or a positive functional study consisting of exercise or pharmacologic stress testing; (2) comparing PCI to OMT; and (3) reporting of at least one of the following outcomes: all-cause mortality, cardiovascular death, nonfatal MI, revascularization, or freedom from angina. We excluded trials enrolling patients who were documented to have had an acute coronary syndrome within 1 week preceding trial entry with the goal of excluding potentially unstable patients. The intervention of PCI was defined as percutaneous transluminal coronary angioplasty with or without bare metal stent or drug-eluting stent (DES) placement. Trials where CABG was used as the revascularization technique were excluded. In 3-arm trials, where OMT was compared with CABG and PCI, only data from the PCI and medical therapy arms was included. Two armed trials where medical therapy was compared with revascularization, and PCI or CABG were not distinctly categorized, were excluded. OMT was defined as a medical regimen consisting of at least an antiplatelet, antianginal, and lipid-lowering therapy.

Selection and Quality Assessment

The results of the searches were compiled using the RefWorks software. After removal of duplicates, reviewers (S.P, F.K, P.K, R.G, N.C) screened each study by title and abstract for inclusion, with each study reviewed by 2 independent reviewers. Those studies that qualified for full text review were again reviewed independently by 2 reviewers for inclusion into the analysis. Two reviewers performed data abstraction (see below) and independently assessed the included studies for sources of systematic bias, as per the Cochrane Handbook for Systematic Reviews of Interventions.[24] Specifically, sequence generation for randomization, allocation concealment, masking of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias including industry funding were assessed in detail. Any disagreements between reviewers were resolved by consensus and if necessary, adjudicated by a third reviewer. For those trials conducted more recently in North America,[16,17] we assessed selective outcome reporting bias by identification of clinical trials through Clinicaltrials.gov to compare a priori outcomes with reported outcomes.

Data Extraction and Synthesis

Two independent reviewers (S.P., F.K.) abstracted data from included studies using a uniform data abstraction form for each study, with the second reviewer reentering data using double-data entry. Data abstracted included study characteristics, patient characteristics, details regarding the intervention and comparison group, and outcome measures. For the primary (all-cause mortality) and each of the secondary (cardiovascular death, nonfatal MI, repeat revascularization, and freedom from angina) outcomes, crude data was collected for the PCI and OMT groups. Where available, outcome data were abstracted at multiple follow-up time points. For trials using survival analysis design, 1-year event rates were extrapolated from the Kaplan-Meier survival curves using the Kaplan-Meier rates, in addition to the final time point data.

Statistical Analysis

Intention-to-treat meta-analysis was performed using the RevMan software provided by Cochrane Collaboration.[25] We assessed heterogeneity by assessing both χ^2 test for heterogeneity and I^2 statistic to determine the proportion of variation attributable to heterogeneity among studies (nonoverlapping CIs or an I^2>50% suggesting significant heterogeneity). The pooled effect estimate was calculated for all included trials on the basis of longest duration of follow-up, and based upon subgroups defined by trial follow-up duration (≤1 year, 1–5 years, and ≥5 years defined as short-, intermediate-, and long-term, respectively) using the Mantel-Haenszel method. Risk ratios for each outcome were calculated using the DerSimonian and Laird random-effects model.[26] Given the heterogeneity in the study design and variability in the definition of optimal medical therapy and PCI use a random-effects model rather than a fixed-effect model was considered more appropriate. Publication bias was estimated visually by funnel plots.

Sensitivity Analyses

A sensitivity analysis evaluating trials with industry funding was conducted to determine potential impact on our summary effect measures. Given the evolution of PCI over the last 2 decades, we also performed a sensitivity analysis to evaluate the potential differential effect of stenting (either bare metal stent or DES) in our comparison of PCI to medical therapy by evaluating separately those studies in which over 50% of participants received stents, as opposed to balloon angioplasty alone. We planned to also perform a sensitivity analysis removing studies of low methodological quality, based upon our bias assessment, but all included studies faired similarly on the risk of bias assessment, most with unknown information regarding allocation concealment and outcome assessor masking. We did not find 1 or more studies to be of significantly greater bias and therefore did not pursue this sensitivity analysis.

Results

Study Selection

We identified 12 randomized clinical trials that fulfilled our inclusion criteria (Figure 1). Enrollment of participants was conducted across the world, with only 2 conducted exclusively in the United States. The trials enrolled a total of 7182 patients who were followed-up for a mean of 4.9 years (range 1.5–10.2 years).

Baseline Characteristics

The baseline characteristics of the included trials are summarized in Table 1 and clinical characteristics of the participants are detailed in Table 2. Enrolled participants were predominantly men, middle aged, and with typical CAD risk factors of hypertension, hyperlipidemia, and diabetes mellitus. Within each trial, baseline characteristics were similar between the PCI and medical therapy groups.

Severity of underlying CAD varied among trials. The Randomized Comparison of Percutaneous Transluminal Coronary Angioplasty and Medical Therapy in Stable Survivors of Acute Myocardial Infarction with Single Vessel Disease: A Study of the Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte (ALKK)[27] and SWISS-II trials enrolled exclusively patients who had a ST segment elevation myocardial infarction within 42 days or 3 months, respectively, in a more stable period after acute MI. However, both trials had excluded those with cardiac events within 1 week of randomization, thus allowing inclusion into our systematic review. A preserved left ventricular ejection fraction was a requirement for most studies, with an left ventricular ejection fraction above 50% in all reported trials.

Inducible or reversible ischemia on stress testing was a prerequisite to study inclusion, with the exception of DEFER,[28,29] where participants with reversible ischemia on noninvasive testing were excluded, presumably due to a favored practice of PCI in this group. The number of affected vessels varied; although the Veterans Affairs Cooperative Study: Angioplasty Compared to Medicine (ACME-1)[30,31] and Medicine, Angioplasty, or Surgery Study (MASS-1)[32,33] enrolled exclusively participants with 1 vessel CAD, the remaining included those with double or triple vessel CAD.

Angioplasty without stenting was performed in majority of included trials. Only the BARI 2D, COURAGE, MASS-2[34,35] and Japanese Stable Angina Pectoris (JSAP)[36] trials performed angioplasty with stenting during PCI in over 50% participants; of those who received stents, generally only a small fraction received DES, whereas the majority of stents placed during

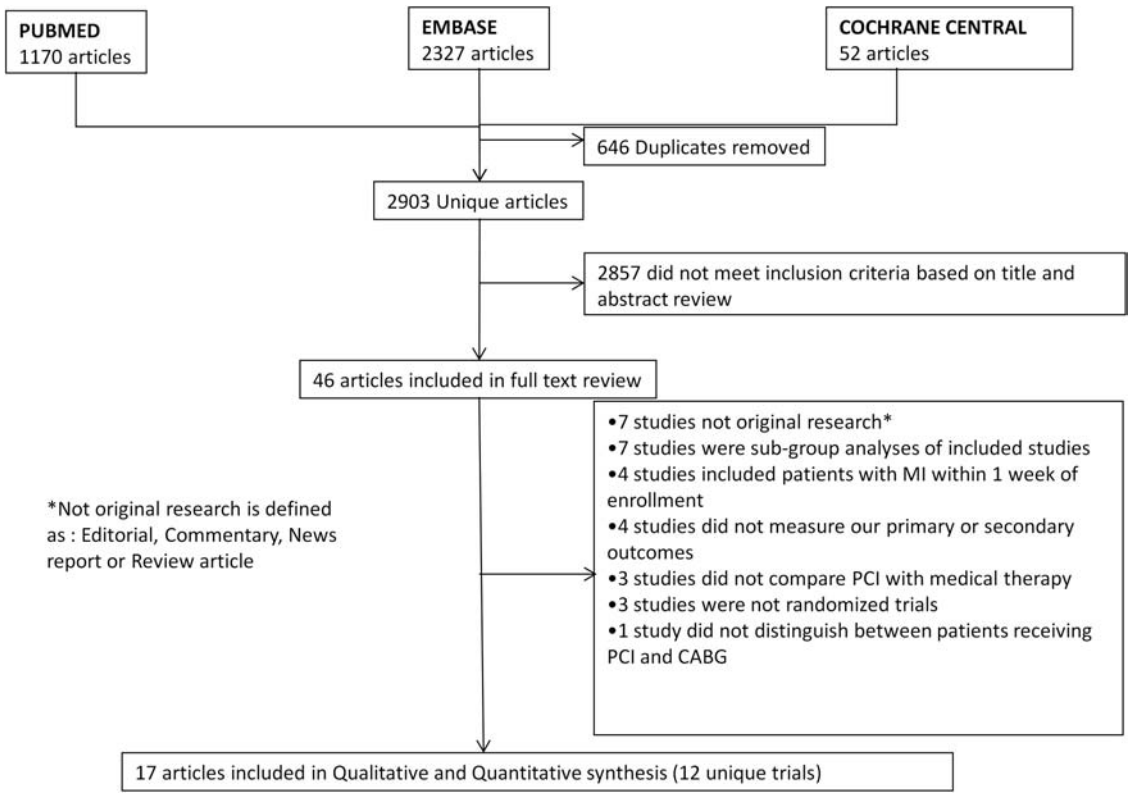

Figure 1. Study selection. The flowchart depicts the selection of studies for inclusion in the meta-analysis. PCI indicates percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass grafting.

Table 1. Characteristics of Included Trials

Study Years of Enrolment, Country or Region	Inclusion Criteria	Exclusion Criteria	Description of Intervention	Description of Medical Therapy	Primary Outcome	Secondary Outcomes	Follow Up, y
ACME-11987–1990 USA	70%–99% stenosis in proximal two thirds of 1 major coronary artery, stress test with ≥1 mm ST depression in at least 1 lead or filling defect on thallium scan, or MI in past 3 mo	Not reported	PTCA	325 mg Aspirin, nitrates, β-blockers, calcium channel blockers	6 mo exercise stress testing: length of time to onset of 1 mm ST depression, maximal ST segment depression, maximal work product	Change in degree of stenosis in index lesion, physical well being questionnaire, employment status	3
ACME-2 1987–1990 USA	History of angina, MI within 3 mo, or ≥3 mm horizontal ST depression on exercise testing; ≥70% stenosis in proximal two thirds of 1 or 2 coronary arteries (data for 1 vessel CAD previously presented as ACME-1)	Unstable angina refractory to medical therapy, prior PCI, primary cardiac diagnosis other than CAD, ≥50% left main stenosis, 3 vessel CAD, LVEF≤30%	PTCA	Aspirin plus individualized therapy of Nitrates, β-blockers, and Calcium channel blockers	Primary/secondary outcomes not individually described Angina frequency, 6 mo exercise tolerance testing and angiography: change in exercise duration, time to onset of angina, maximal rate-pressure product, percent diameter stenosis of index lesions		Median 5
ALKK 1994–1997, Germany	Post STEMI 8–42 d with feasible PTCA or recanalization of culprit artery, CCS Class I or II angina	CCS Class III or IV angina, >70% stenosis in another coronary artery, CABG graft as infarct vessel, need for CABG (left main stenosis, LV aneurysm, significant valve disease), noncardiac disease reducing life expectancy	PTCA, BMS	100 mg aspirin, β-blockers, and additional medications per physician discretion	Composite of survival free of reinfarction, ischemia driven PCI or CABG, or rehospitalization for severe angina at 1 y	Recurrent MI or revascularization at long-term follow-up (≈5 y)	Mean 4.7
AVERT 1995–1996, North America, Europe	≥50% stenosis of at least 1 coronary artery for which PCI was recommended, asymptomatic or with CCS I or II angina, completion of at least 4 min of stress test without ischemia, LDL≥115 mg/dL, and triglycerides <500 mg/dL	Left main disease, 3 vessel CAD, unstable angina, MI in prior 2 wk, LVEF<40%	PTCA, BMS, atherectomy	80 mg atorvastatin	Composite of ischemic event, which included cardiac death, resuscitation after cardiac arrest, nonfatal MI, stroke, PCI, CABG, and worsening angina requiring hospitalization	Individual components of primary endpoint	1.5
BARI 2D 2001–2005 North and South America, Europe	≥50% stenosis of major coronary artery with positive stress test or ≥70% stenosis of major coronary artery with classic angina and type 2 diabetes mellitus	Need for immediate revascularization, left main disease, creatinine >2 mg/dL, glycated hemoglobin >13%, class III or IV heart failure, hepatic dysfunction, PCI, or CABG in previous 12 mo	PTCA, BMS, DES	Aspirin, statins, β-blockers, andACE or ARB; insulin and oral hypoglycemic therapy	All-cause mortality	Composite of all-cause mortality MI, or stroke	5

(*Continued*)

Table 1. (Continued)

Study Years of Enrolment, Country or Region	Inclusion Criteria	Exclusion Criteria	Description of Intervention	Description of Medical Therapy	Primary Outcome	Secondary Outcomes	Follow Up, y
COURAGE 1999–2004 North America	≥70% stenosis in at least 1 proximal artery, inducible ischemia on stress testing or ST depression or TWI on resting EKG	CCS class IV angina, substantial ST depression or hypotension during Bruce protocol stage 1 stress testing, refractory heart failure or cardiogenic shock, LVEF <30%, revascularization in prior 6 mo, coronary anatomy not suitable for PCI	PTCA, BMS, DES	81–325 mg aspirin and 75 mg copidogrel; long-acting metoprolol and amlodipine and nitrates; lisinopril or losartan; simvastatin alone or with ezetimibe; extended-release niacin and fibrates if needed	Composite of all-cause mortality and nonfatal MI	Composite of all-cause mortality, MI, stroke, and hospitalization for unstable angina; angina functional class (CCS scale); Quality of life; resource use; cost effectiveness	Median 4.6
DEFER 1997–1998 Europe, Asia	Angiography with >50% stenosis in native coronary artery and FFR ≥0.75, no evidence of reversible ischemia by noninvasive testing within the previous 2 mo	Total occlusion of the target artery, Q-wave infarction, unstable angina, or small target arteries	PTCA, BMS	Statins, β-blockers, nitrates	Composite of all-cause mortality, MI, CABG, PCI, and any procedure-related complication requiring major intervention or prolonged hospital stay	Freedom from angina (CCS I) and the use of antianginal drugs	2
JSAP 2002–2004 Japan	≥75% (or ≥60% on quantitative coronary angiography) 1 or 2 vessel CAD, inducible ischemia on stress testing or ST depression or T-wave inversion on resting EKG	Three vessel CAD, left main or ostial LAD disease, total occlusion, ACS, LVEF <50%, tendency to bleed, disseminated intravascular coagulation, severe pneumonia, creatinine >1.5 mg/dL, graft stenosis, low-risk CAD where PCI or medical therapy had already been prescribed	PTCA, BMS	Entirely physician-dependent (majority received aspirin or other antiplatelet, β-blockers, nitrates, Statins, ACE/ARB)	Composite of all-cause mortality, ACS, stroke, emergent hospitalization requiring intensive care	Angina functional class (CCS scale), elective repeat revascularization	3.3
MASS-11 988–1991 Brazil	≥80% LAD stenosis before takeoff of first diagonal branch, single vessel CAD	Total occlusion, lesion length >12 mm, involvement of the ostium, heavy calcification, severe tortuosity, left main disease, unstable angina, prior MI, significant valvular disease, cardiomyopathy, LV dysfunction, prior PCI or CABG	PTCA	Aspirin, nitrates, β-blockers	Composite of cardiac death, MI, or refractory angina requiring revascularization; surgical revascularization in PCI group	Angina functional class (CCS scale), employment status, positive stress test 2 y after enrolment, degree of CAD at 2 y angiographic follow-up	5

(*Continued*)

Table 1. (Continued)

Study Years of Enrolment, Country or Region	Inclusion Criteria	Exclusion Criteria	Description of Intervention	Description of Medical Therapy	Primary Outcome	Secondary Outcomes	Follow Up, y
MASS-2 1995–2000 Brazil	≥70% proximal multivessel stenosis and documented ischemia by stress testing or CCS II or III	Unstable angina, acute MI requiring emergent revascularization, ventricular aneurysm requiring surgical repair, LVEF<40%, prior PCI or CABG, single vessel CAD, congenital heart disease, valvular heart disease, cardiomyopathy, left main stenosis ≥50%, unable to comply with protocol or follow up, suspected or known pregnancy	PTCA, BMS, lasers, atherectomy	Aspirin, nitrates, β-blockers, calcium channel blockers, ACE inhibitors, statins	Composite of cardiac death, MI, or refractory angina requiring revascularization	Freedom from angina and stroke	5
RITA-2 1992–1996 United Kingdom and Ireland	Angiography with ≥50% (2 views) or ≥70% (1 view) stenosis in at least 1 major artery amenable to PTCA, recent unstable angina at least 7 d before randomization	Revascularization necessary for symptom relief or prognostic benefit, prior revascularization, significant left main disease, ACS in the previous 7 d, hemodynamically significant valve disease, or life-threatening noncardiac disease	PTCA; BMS or atherectomy if PTCA unsatisfactory	Aspirin, β-blockers, calcium channel blockers, long acting nitrates at maximally tolerated doses, lipid-lowering drugs only as needed	Composite of all-cause mortality and nonfatal MI	Revascularization with PCI or CABG, heart failure, arrhythmia, stroke, or transient ischemic attack	7
SWISS-2 1991–1997 Switzerland	First STEMI or non-STEMI within 3 preceding mo, no malignancy, 1–2 vessel CAD on angiography and silent ischemia on maximal exercise stress testing with imaging	3 vessel CAD, coronary lesions not technically amenable to PCI	PTCA	100 mg aspirin, statin, 5–10 mg bisoprolol, 5–10 mg amlodipine, 4–12 mg BID Molsidomine; ACE inhibitor if HTN	Composite of cardiac death, nonfatal recurrent MI (including silent MI) and symptom-driven revascularization with PCI or CABG	Individual components of primary outcome and noncardiac death, all-cause death, angina not leading to revascularization	Mean (SD)10.2 (2.6)

ACE indicates angiotensin converting enzyme; ACME, Angioplasty Compared to Medicine; ACS, acute coronary syndrome; ALKK, Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; ARB, angiotensin receptor blocker; AVERT, Atorvastatin vs revascularization treatment; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; BMS, bare metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian classification system; COURAGE, Clinical Outcomes Utilizing Revascularization; DES, drug eluting stent; DBP, diastolic blood pressure; FFR, fractional flow reserve; HTN, hypertension; JSAP, Japanese Stable Angina Pectoris; LAD, left anterior descending; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RITA, Randomized Intervention Treatment of Angina; SBP, systolic blood pressure; STEMI, ST-Segment–Elevation Myocardial Infarction; SWISS, Swiss Interventional Study on Silent Ischemia.

Table 2. Baseline Patient Characteristics

	ACME-1		ACME-2		ALKK		AVERT		BARI 2D		COURAGE		DEFER		JSAP		MASS-1		MASS-2		RITA-2		SWISS-2	
	PCI	OMT	PCI	OMT	PCI	OMT	PCI	PCI	PCI	OMT	PCI	OMT	PCI	OMT	PCI	OMT	PCI	OMT	PCI	OMT	PCI	OMT	PCI	OMT
Number randomized	105	107	51	50	149	151	90	90	798	807	1149	1138	90	91	192	192	72	72	205	203	504	514	96	105
Mean age in y (SD)	62	63	60		58.2 (9.2)	57.5 (9.8)	58(0.6)	61(11)	61(11)	62.4(9.0)	61.5 (10.1)	61.8 (9.7)	61 (11)	61 (9)	64.5 (7.2)	64.2 (7.6)	54 (9)	58 (7)	60(9)	60(9)	5		54.4 (9.1)	56.2 (8.8)
Male, %	100	100	100		84	89	89	63	63	67	85	85	63	65	75	75	81	82	85	84	82	83	89	87
Diabetes mellitus, %	17	19	18		15	17	15	9	9	100	32	35	9	15	40	40	15	20	11	18	10	8	9	13
Hypertension, %	52	53	NR		32	46	45	34	34	82	66	67	34	36	63	63	34	38	30	27	NR	NR	45	45
Prior MI, %	33	28	45		100	100	40	21	21	30	38	39	21	29	14	15	0	0	25	19	47	46	100	100
Baseline LVEF (SD)	64.9 (1.1)	65.1 (1.3)	67		NR	NR	61	66(7)	66(7)	NR	60.8 (11.2)	60.9 (10.3)	66 (7)	65 (9)	64(9.7)	65.8 (9.6)	77(6)	74(4)	67(8)	68(7)	NR	NR	53.9 (9.9)	59.7 (11.8)
Mean SBP (SE) in mm Hg	134	137	NR		NR	NR	NR	NR	NR	131(20)	131(0.8)	130(0.7)	NR	NR	142 (25)	140 (24)	NR	NR	NR	NR	NR	NR	128.8 (21.8)	127.2 (21.0)
Mean DBP (SE) in mm Hg	79	82	NR		NR	NR	NR	NR	NR	74(11)	74(0.3)	74(0.3)	NR	NR	73 (12)	73 (13)	NR	NR	NR	NR	NR	NR	76.3 (15.2)	77.6 (13.6)
Mean LDL (SD) in mg/dL	108	105	NR		NR	NR	143	NR	NR	97	100(1.2)	102(1.2)	NR	NR	125 (32)	116 (32)	141 (42)	162 (36)	148 (34)	149 (34)	NR	NR	NR	NR
% with 1/2/3 vessel CAD	100/0/0		0/100/0		NR		56/44/0	57/43/0	45/35/20	68/29/3	68/29/3	30/39/31	68/ 29/ 3	65/ 27/ 8	68/32/0	68/31/0	100/ 0/0	100/ 0/0	0/21/28	0/20/29	62/32/6	58/34/8	2.0* (1.0)	2.3* (1.3)
Stenting of PCI group at randomization, %	0		0		17		30		91		88		46		76		0		72		8		0	
Medication usage, %																								
Aspirin	85	91	NR	NR	NR	NR	26	16	88	88	100	95	NR	NR	92	91	NR	NR	80	80	87	87	NR	NR
Statin	NR	NR	NR	NR	NR	NR	10	93	76	74	86	89	37†	37†	49	45	NR	NR	73	68	14†	12†	NR	NR
Other anti-lipid agent	NR	NR	NR	NR	NR	NR	19	26	15	16	8	8			6	7	NR	NR	NR	NR			NR	NR
β-blocker	30	50	NR	NR	74	75	69	62	72	71	85	89	62	71	44	52	NR	NR	61	68	68	65	NR	91
Nitrates	24	50	NR	NR	72	80	57	57	28	33	62	72	53	56	51	57	NR	NR	41	73	46	41	NR	63
ACE or ARB	NR	NR	NR	NR	NR	NR	8	9	76	79	58	60	NR	NR	20	25	NR	NR	30	29	9	11	NR	NR

ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; AVERT, Atorvastatin versus Revascularization Treatment; BARI, Bypass Angioplasty Revascularization Investigation; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Trial of unstable Angina; SWISS, Swiss Interventional Study on Silent Ischemia; PCI, percutaneous coronary intervention; OMT, optimal medical therapy; LVEF, left ventricular ejection fraction; NR, not reported; SBP, systolic blood pressure; MI, myocardial infarction; LDL, low-density lipoprotein; CAD, coronary artery disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure.

*Mean number of vessels.

†Any lipid lowering therapy (statin or nonstatin).

the time of these trials were bare metal stent. BARI 2D, thew most recent of the trials included in this review, used DES in over one third of participants in the PCI group.

Medical regimens varied too, though, where reported, nearly all participants were taking at least a daily baby aspirin and most were on antianginal therapy with nitrates and β-blockers. Mean blood pressure and low-density lipoprotein values varied depending on the timing of the trial, due to the evolution of stricter targets (Table 2). Statin use varied with the more recent trials, namely COURAGE, MASS-2, and SWISS-II, reporting statin use in majority of participants. The Atorvastatin versus Revascularization Treatment (AVERT)[37] trial, which was designed specifically to compare atorvastatin with PCI, used statins in all enrolled participants. With the exception of the AVERT trial, which used high dose atorvastatin, the other trials did not explicitly comment on statin dosing. Of note, medical therapies were, for the most part, used uniformly in both the PCI and medical therapy groups of each of the included trials. One exception was ACME-1, where all antianginal therapies were discontinued in the PCI group before study entry.

Of the trials reporting freedom from angina measures, most used the Canadian Cardiovascular Society classification system,[38] whereas the ACME-1 and ACME-2[39] trials exclusively used self-reported frequency of angina events and time to angina on exercise testing.

Outcomes

All Cause Mortality

Overall, there was no statistically significant difference in mortality between the PCI and OMT groups; the point estimate at the longest follow-up duration notably did favor the PCI group (risk ratio [RR], 0.85; 95% CI, 0.71–1.01) (Figure 2). Effect measures at the ≤1 year (RR, 1.34; 95% CI, 0.87–2.08) and 1 to 5 years (RR, 0.97; 95% CI, 0.56–1.69) time points showed no significant difference in mortality between the PCI and OMT groups, and a trend towards benefit with PCI was most apparent at the ≥5 years follow-up duration (RR, 0.82; 95% CI, 0.65–1.02). In the longest duration of follow-up, SWISS-2 and ALKK individually showed the most favorable effects of PCI over OMT; of note, these 2 trials included those with prior recent MIs. The studies given greatest statistical weight in this analysis, BARI-2D and COURAGE, showed no significant difference in all-cause mortality between the 2 groups.

Cardiovascular Death

There was no statistically significant difference in cardiovascular death between the PCI and OMT groups (Figure 3). The point estimate in the longest follow-up duration analysis favored the PCI group (RR, 0.71; 95% CI, 0.47–1.06), and this difference was most apparent in those trials with ≥5 years follow-up (RR, 0.70; 95% CI, 0.46–1.08) although these were not statistically significant. In those trials with <5 years follow-up, there was no significant difference in this outcome between the 2 groups (RR, 1.53; 95% CI, 0.69–3.38).

Nonfatal MI

We observed no difference in nonfatal MI between the PCI and OMT groups in the overall analysis (RR, 0.93; 95% CI, 0.70–1.24) and at each of the follow-up time points (Figure 4). For the ≤1 year, 1 to 5 years, and ≥5 year time points, we observed a RR, 0.82; (95% CI, 0.37–1.80), RR, 1.11; (95% CI, 0.47–2.59), and RR, 0.92; (95% CI, 0.67–1.27), respectively.

Revascularization

There was no difference in symptom-driven subsequent revascularization in the overall analysis (RR, 0.93; 95% CI, 0.76–1.14) and at all time points (≤1 year, 1–5 years, and ≥5 year time points, respectively: RR, 1.49; 95% CI, 0.71–3.16; RR, 0.98; 95% CI, 0.74–1.30; RR, 0.99; 95% CI, 0.75–1.30) (Figure 5). There was notably significant statistical heterogeneity among trials included in this analysis at all time points. The older MASS-1 and ACME trials were outliers showing greater proportion of early repeat PCI or CABG required in the PCI group, possibly due to less experience and more complications during this era.

Freedom From Angina

Overall, PCI was associated with a greater freedom from angina as compared with OMT (RR, 1.20; 95% CI, 1.06–1.37) (Figure 6). This benefit with PCI was evident at all follow-up durations (≤1 year, 1–5 years, and ≥5 year time points, respectively: RR, 1.32; 95% CI, 1.13–1.54; RR, 1.57; 95% CI, 1.06–2.32; RR, 1.17; 95% CI, 1.00–1.38).

Sensitivity Analysis

Only the AVERT trial was clearly industry sponsored, and sponsorship of DEFER was not reported. Removal of these studies showed no difference in overall mortality (RR, 0.82; 95% CI, 0.67–1.01).

BARI-2D, COURAGE, JSAP, and MASS-2 were the only trials to report over 50% stent use in the PCI arm. Considering only these trials, there was no significant difference in all-cause mortality (0.93; 95% CI, 0.78–1.11). Analysis by trial follow-up duration also revealed no significant difference (at the short-, intermediate, and long-term time points, respectively: RR, 1.48; 95% CI, 0.86–2.55; RR, 0.87; 95% CI, 0.30–2.54; and RR, 0.93; 95% CI, 0.78–1.12).

Risk of Bias

All included trials were published randomized clinical trials. Method of randomization was adequately described (computer generated or automated telephone system) in approximately half of the trials and allocation concealment was only explicitly reported in 1 trial. Masking of outcome assessors was described in the more recent trials (Randomized Intervention Trial of unstable Angina [RITA]-2,[40,41] BARI-2D, JSAP, SWISS-2). Losses to follow-up were reported in all trials and with the exception of the ACME trials, where angina data at the final interview are missing, these participants encompassed <10% of total study participants. Intention-to-treat analysis was used in all trials. Most trials were free of selective outcome reporting and in addition, outcomes were predefined in the methods section of most included trials. The risk of bias across all studies is summarized in online-only Data Supplement, Figure I. Publication bias was assessed with the use of a funnel plot to address the primary outcome of all-cause mortality (online-only Data Supplement Figure II), with symmetry of the plot indicating no clear relationship in lack of publication by size of trial and effect estimate.

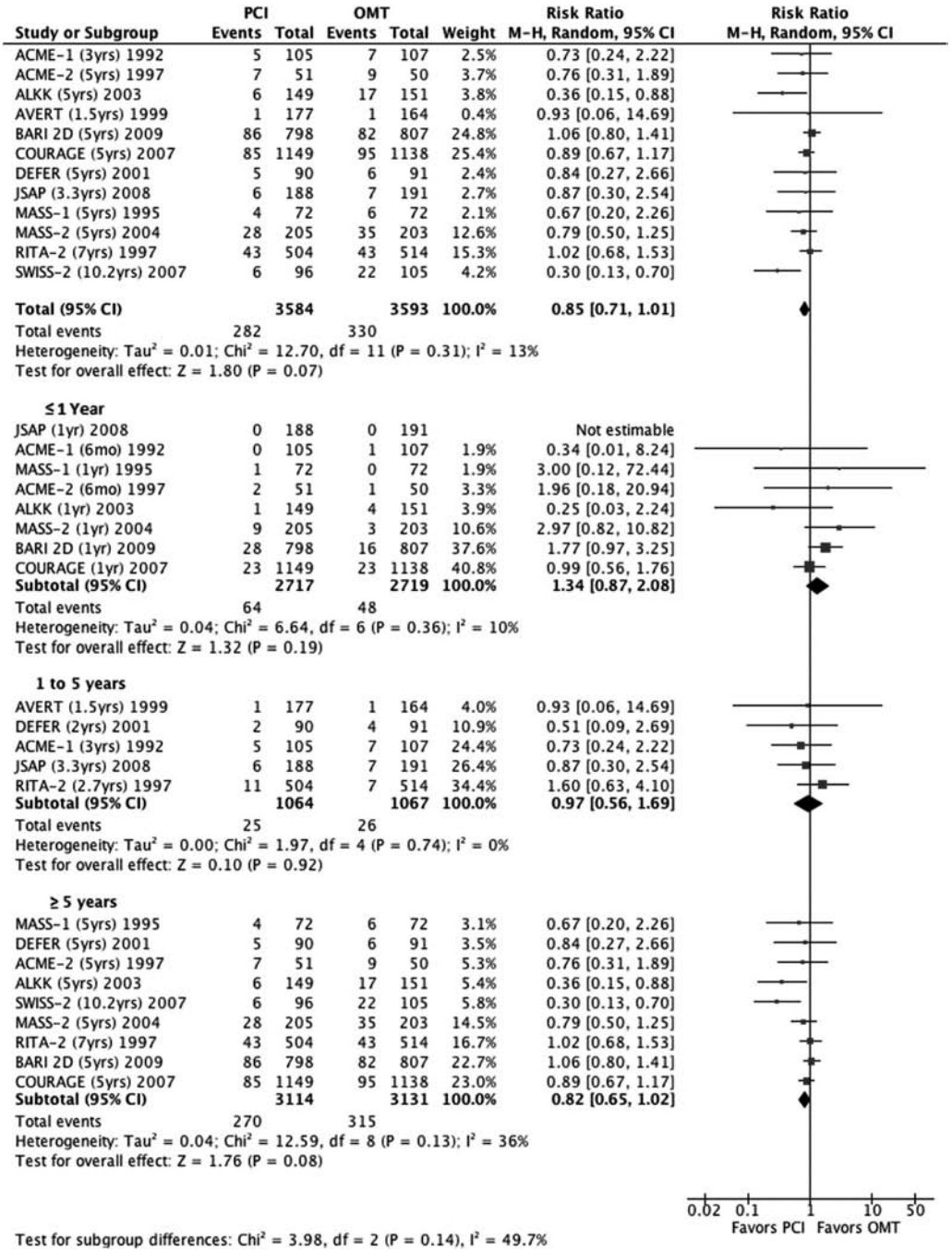

Figure 2. Percutaneous coronary intervention (PCI) vs optimal medical therapy (OMT) for the risk of all-cause mortality. The forrest plot depicts the individual trial and subtotal risk ratios and 95% CIs comparing the outcome of all-cause mortality for PCI vs OMT. The first plot shows the overall analysis, using available data for the longest duration of follow up, and subsequent plots are stratified by trial follow-up duration. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; AVERT, Atorvastatin versus Revascularization Treatment; BARI, Bypass Angioplasty Revascularization Investigation; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Trial of unstable Angina; SWISS, Swiss Interventional Study on Silent Ischemia.

Discussion

In this most updated analyses to-date, we observed no significant difference in outcomes of all-cause mortality, cardiovascular death, nonfatal MI, or need for symptom-driven subsequent revascularization with PCI when compared with OMT alone. However, the point estimate for all-cause mortality and cardiac death favored PCI and was most prominent in trials with longer duration of follow up, but was attenuated when the analyses were restricted to trials where stents were used. PCI, was associated with a greater freedom from angina in the overall analysis and at all studied time points.

In comparison to the meta-analysis published by Schömig et al, we added several large trials published in the interim (JSAP and BARI 2D). In addition, we used more stringent criteria in establishing a population of individuals with stable

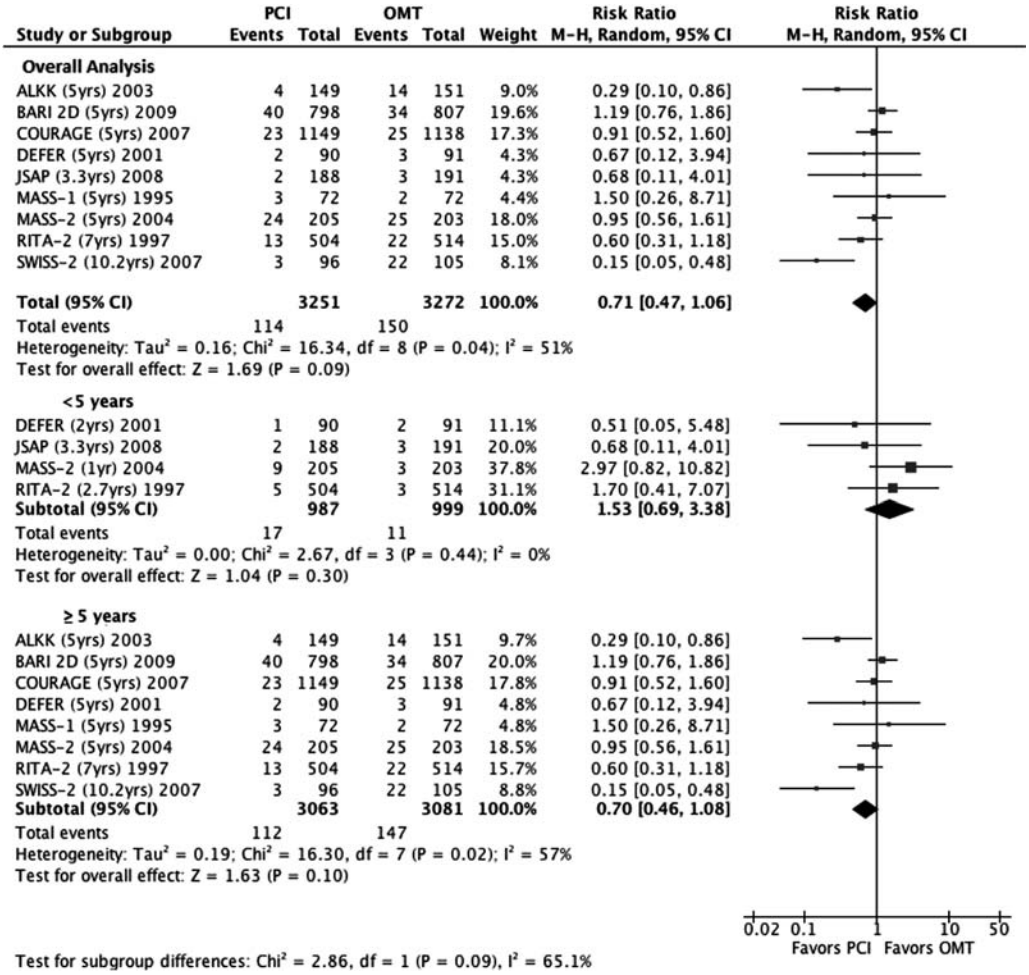

Figure 3. Percutaneous coronary intervention (PCI) vs optimal medical therapy (OMT) for the risk of cardiac death. The forrest plot depicts the individual trial and subtotal risk ratios and 95% CIs comparing the outcome of cardiac death for PCI vs OMT. The first plot shows the overall analysis, using available data for the longest duration of follow up, and subsequent plots are stratified by trial follow-up duration. ALKK indicates Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; BARI, Bypass Angioplasty Revascularization Investigation; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Trial of unstable Angina; SWISS, Swiss Interventional Study on Silent Ischemia.

CAD, excluding those studies that included participants with an MI <1 week before enrollment.[42,43] We also excluded studies that compared revascularization, defined as PCI or CABG, with medical therapy, in our aim to evaluate only nonsurgical revascularization.[44–46] We excluded a study designed to compare revascularization with an exercise training program[47] and a study in abstract form,[48] where detailed methods could not be verified. Finally, we also evaluated the clinically meaningful outcomes of symptom-driven revascularization and freedom from angina. A prior analysis[20] evaluating angina relief showed a similar benefit of PCI over OMT, although this meta-analysis notably included 4 trials that enrolled recent MI survivors. All outcomes in our analyses, as compared with prior analyses, were additionally stratified by time duration of follow-up.

It must be noted that there exists no standard definition for stable CAD. The trials included in this meta-analysis had varying angiographic definitions for significant coronary stenosis and only a minority clearly described a requirement for clinical symptoms of angina. Exclusion of trials enrolling participants within 1 week of an acute coronary syndrome aimed to identify a population of stable CAD patients. The ALKK and SWISS-2 trials notably fulfilled the inclusion criteria for this meta-analysis, but all participants had a recent MI, and therefore, may not reflect the same population of stable CAD patients included in the other trials.

Inclusion of trials published over the course of 2 decades notably presents considerable heterogeneity. Older trials used balloon angioplasty only, which has since proven to be inferior to angioplasty with stenting, due to high rates of subsequent restenosis.[49,50] In addition, newer generation DES have been shown to be not only efficacious in having a very low rate of restenosis but also safe, with reduction in MI when compared with bare metal stents.[51] Of note, only the COURAGE, MASS-2, JSAP, and BARI 2D trials used stents in the majority of participants and only COURAGE and BARI-2D used DES. It is therefore unknown whether the results of the present study can be extrapolated to contemporary cohorts. Moreover, medical therapies have advanced, with usage of high dose statins and antiplatelet therapy as standard of care. Our sensitivity analysis of studies in which

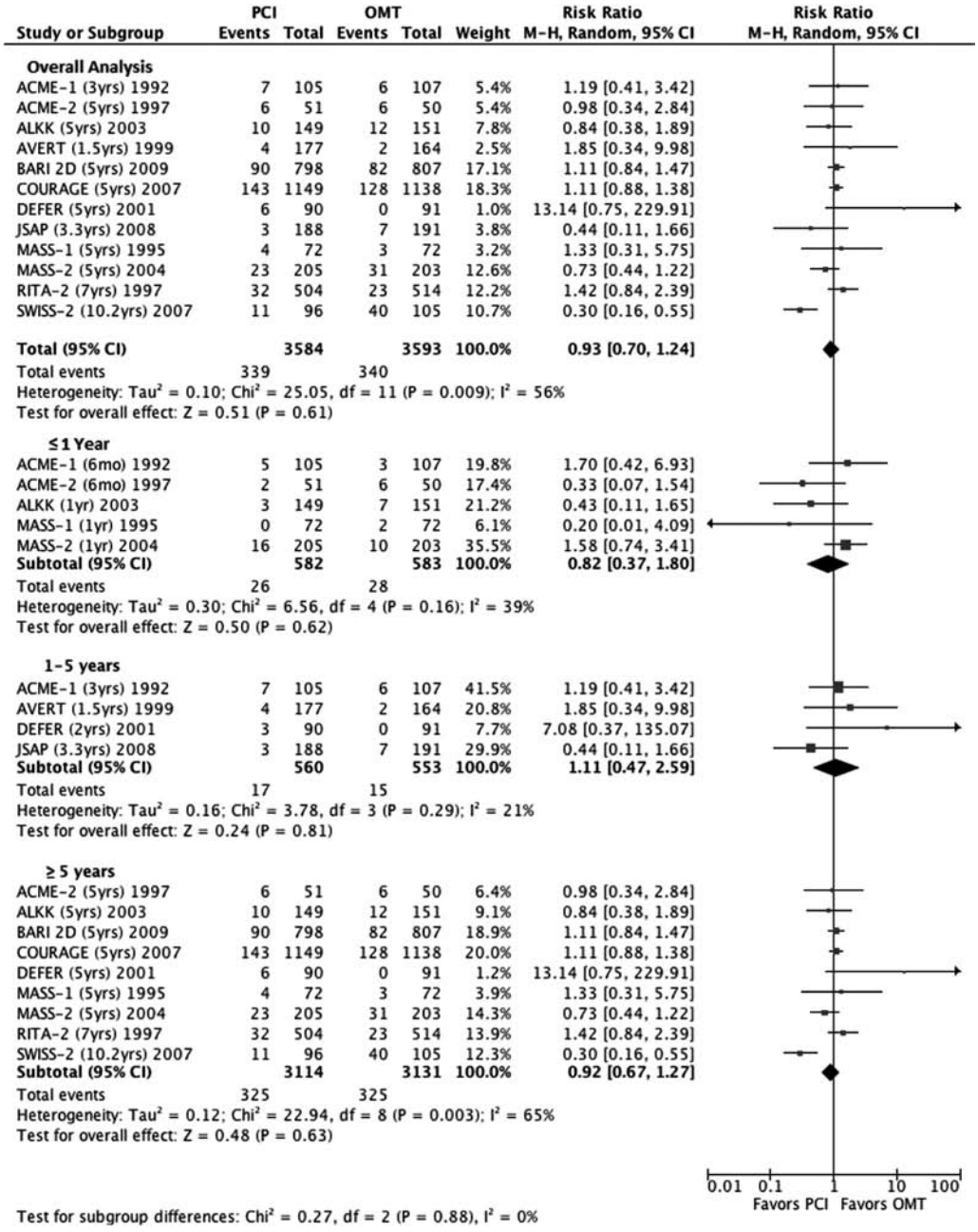

Figure 4. Percutaneous coronary intervention (PCI) vs optimal medical therapy (OMT) for the risk of nonfatal myocardial infarction (MI). The forrest plot depicts the individual trial and subtotal risk ratios and 95% CIs comparing the outcome of nonfatal MI for PCI vs OMT. The first plot shows the overall analysis, using available data for the longest duration of follow up, and subsequent plots are stratified by trial follow-up duration. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; AVERT, Atorvastatin versus Revascularization Treatment; BARI, Bypass Angioplasty Revascularization Investigation; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Trial of unstable Angina; SWISS, Swiss Interventional Study on Silent Ischemia.

>50% stent use was performed, which were the more recently published trials, notably revealed no significant difference in all-cause mortality. This lack of difference perhaps emphasizes advancements and increasing use of effective medical therapies for patients with stable CAD. Yet, it must be noted that even the most recent trials in this meta-analysis do not use newer generation DES, do not achieve current guidelines for low-density lipoprotein targets, and do not demonstrate uniformly high usage of statin, β-blocker, and antianginal medications (Table 2).

The types of participants enrolled notably were heterogeneous, and generalization of effect measures to dissimilar populations should be undertaken with caution. Although we aimed to identify stable CAD participants, ALKK and SWISS-2 evaluated exclusively those individuals who had an MI roughly within 1 month before enrollment; PCI in these 2 studies appeared protective. Severity of CAD based on number of vessels involved also varied; COURAGE and MASS-2 notably included a high proportion of patients with triple vessel CAD, where surgical revascularization options must also be considered.

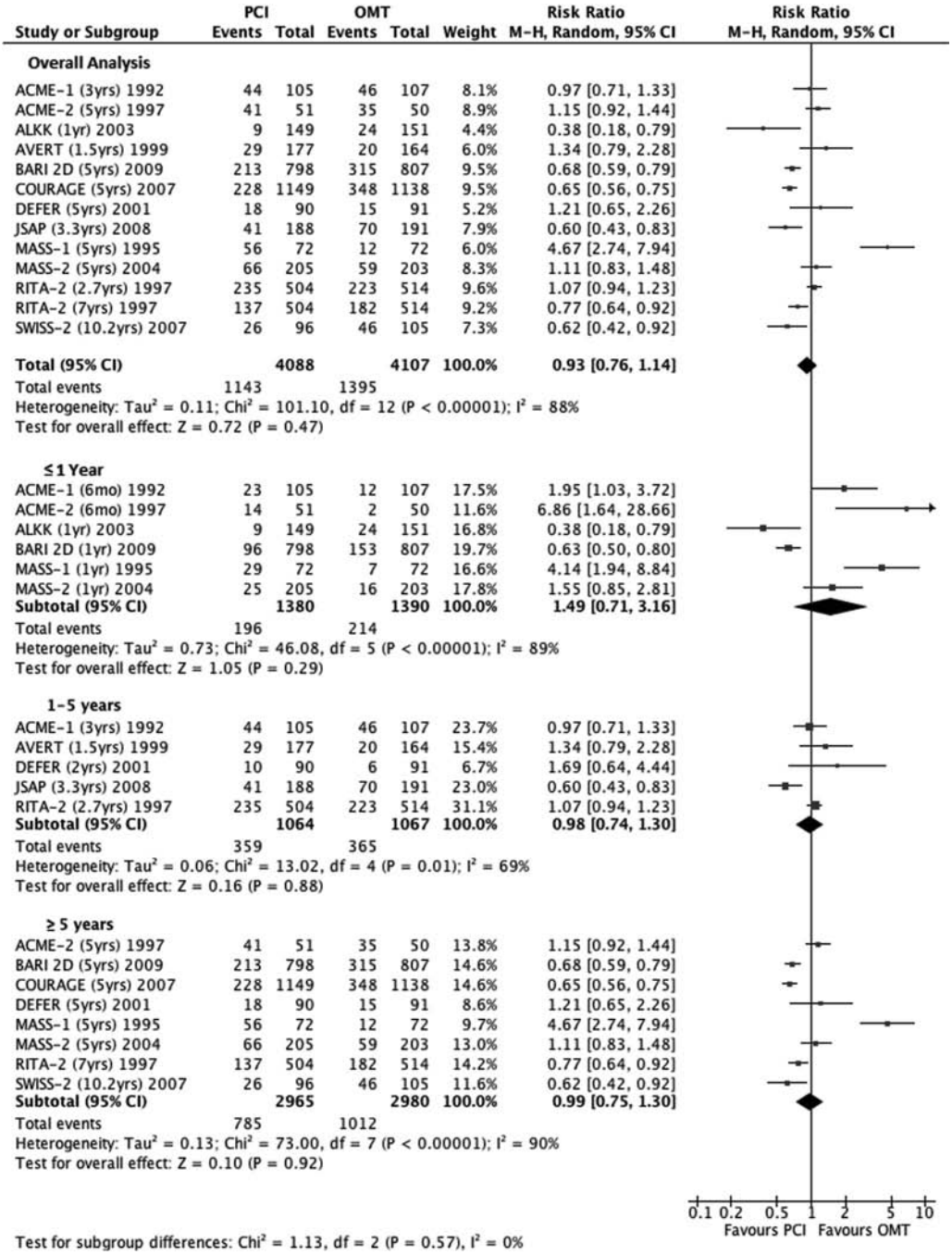

Figure 5. Percutaneous coronary intervention (PCI) vs optimal medical therapy (OMT) for the risk of revascularization. The forrest plot depicts the individual trial and subtotal risk ratios and 95% CIs comparing the outcome of revascularization for PCI vs OMT. The first plot shows the overall analysis, using available data for the longest duration of follow up, and subsequent plots are stratified by trial follow-up duration. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; AVERT, Atorvastatin versus Revascularization Treatment; BARI, Bypass Angioplasty Revascularization Investigation; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Trial of unstable Angina; SWISS, Swiss Interventional Study on Silent Ischemia.

Study Limitations

We recognize several limitations to our analysis. Analysis of symptom-driven revascularization and freedom from angina outcomes is subjective and is also prone to reporting bias by providers and participants, respectively. As in other analyses, we were not able to adjust our analysis for the dosage of medications administered on the proportion of patients with stent usage, and are best assessed with an individual patient level meta-analysis. To complement our sensitivity analysis of those studies reporting >50% stent use in the PCI group, we would have preferred also to pursue an analysis of OMT, based upon contemporary guidelines. Given the evolving nature of medical therapies and variations in blood pressure and cholesterol targets at the time of the individual trials, such an analysis could not be pursued due to marked heterogeneity.

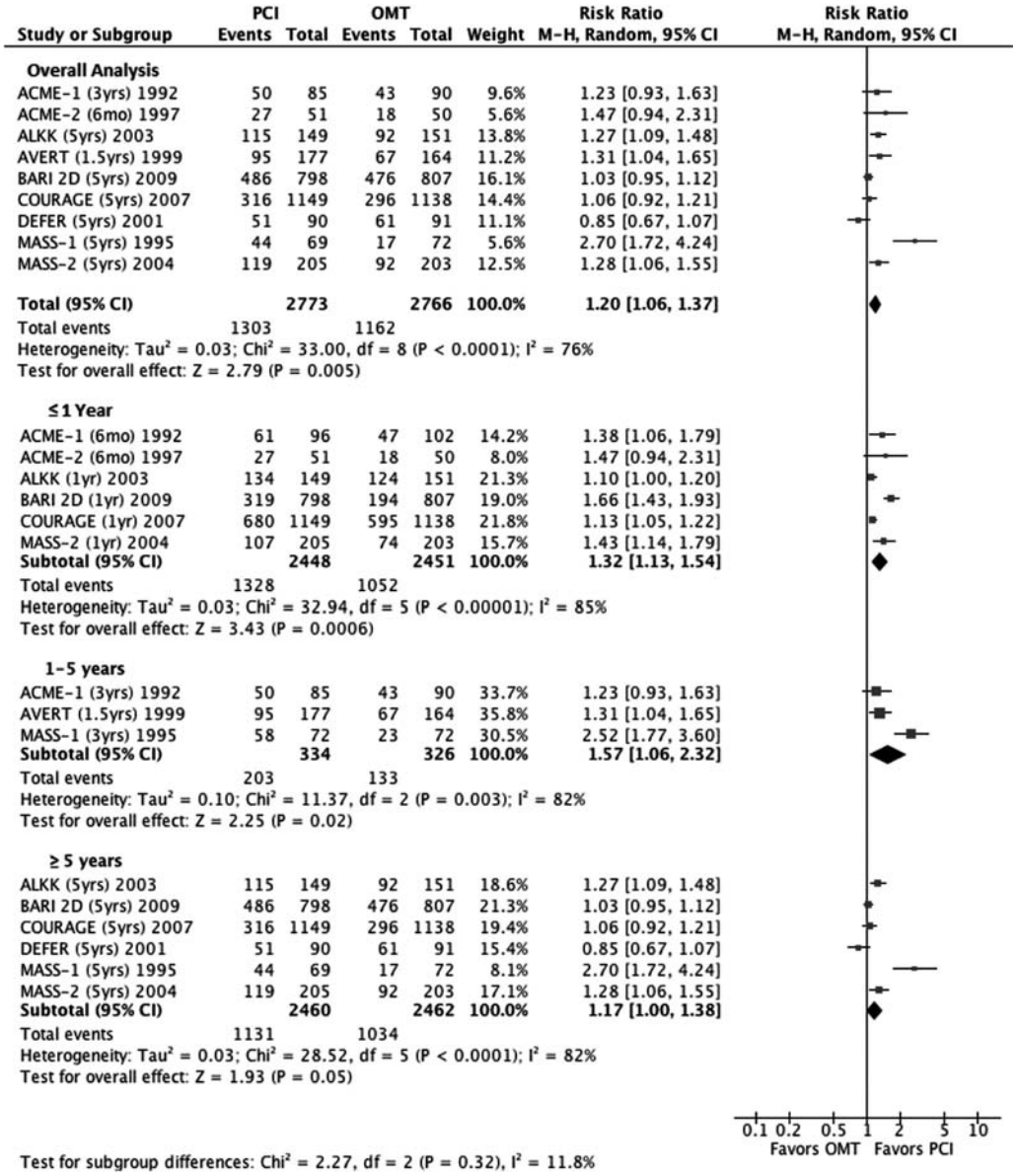

Figure 6. Percutaneous coronary intervention (PCI) vs optimal medical therapy (OMT) for the risk of freedom from angina. The forrest plot depicts the individual trial and subtotal risk ratios and 95% CIs comparing freedom from angina for PCI vs OMT. The first plot shows the overall analysis, using available data for the longest duration of follow up, and subsequent plots are stratified by trial follow-up duration. ACME indicates Angioplasty Compared to Medicine; ALKK, Arbeitsgemeinschaft Leitended Kardiologische Krankenhausarzte; AVERT, Atorvastatin versus Revascularization Treatment; BARI, Bypass Angioplasty Revascularization Investigation; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Stable Angina Pectoris; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Trial of unstable Angina; SWISS, Swiss Interventional Study on Silent Ischemia.

Conclusions

In summary, in patients with stable CAD there is no definitive evidence of an added benefit of PCI to reduce the risk of mortality, cardiac death, nonfatal MI, and need for revascularization, when compared with medical therapy alone. PCI appeared to show a benefit for all-cause mortality and cardiac death that was attenuated when recent studies (with more aggressive medical therapy) with a high proportion of stent use were analyzed. However, PCI provides a benefit over medical therapy in symptom relief of angina in patients with stable CAD.

A greater understanding of the pathophysiology of atherosclerosis has led to advancements in PCI with the advent of DES and improvements in medical therapies. In addition, the prior strategy trials have been criticized for enrolling participants after cardiac catheterization (creating selection bias), enrolling lower risk individuals (without significant ischemia) and with the use of DES (only first generation) in a small fraction of the cohort. Ongoing trials, such as the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA),[52] will test treatment strategies upstream of cardiac catheterization and involve patients with at least moderate ischemia, with the use of contemporary optimal medical and optimal revascularization strategies, with a sample size (N =8000) large enough to detect small differences in outcomes.

Disclosures

None.

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