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Systematic Review/Meta-analysis

A Meta-analysis of Randomized Controlled Trials Comparing Percutaneous Coronary Intervention With Medical Therapy in Stable Angina Pectoris

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See editorial by Waters, pages 411-414 of this issue.

ABSTRACT

There continues to remain uncertainty regarding the effect of percutaneous coronary intervention (PCI) vs medical therapy in patients with stable angina. We therefore performed a systematic review and study-level meta-analysis of randomized controlled trials of patients with stable angina comparing PCI vs medical therapy for each of the following individual outcomes: all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), and angina relief. We used 8 strategies to identify eligible trials including bibliographic database searches of MEDLINE, PubMed, EMBASE, and the Cochrane Controlled Trials Registry until November 2011. Two independent reviewers undertook decisions about study eligibility and data abstraction. Data were pooled using a random effects model. Ten prospective randomized controlled trials fulfilled our eligibility criteria and they included a

RÉSUMÉ

L'incertitude concernant l'effet de l'intervention coronarienne percutanée (ICP) par rapport au traitement médical chez les patients ayant une angine stable demeure. Par conséquent, nous avons effectué une revue systématique et une méta-analyse d'essais aléatoires de patients ayant une angine stable en comparant l'ICP au traitement médical pour chacun des résultats individuels suivants : la mortalité toutes causes confondues, la mortalité cardiovasculaire (CV), l'infarctus du myocarde (IM) et le soulagement de l'angine. Nous avons utilisé 8 stratégies pour déterminer les essais admissibles incluant les recherches de bases de données bibliographiques de MEDLINE, de PubMed, d'EMBASE et du Registre des essais Cochrane jusqu'au mois de novembre 2011. Deux (2) examinateurs indépendants ont pris les décisions sur l'admissibilité de l'étude et l'abstraction de données. Les

Coronary artery disease (CAD) is the leading cause of death and disability worldwide resulting in 7.2 million deaths per year.[1] In the United States alone, it affects 16,800,000 people resulting in 450,000 deaths annually.[2] Important advances in medical therapy have significantly improved the prognosis of these patients. These advances include the more widespread use of disease-modifying secondary prevention therapies (eg, statins, inhibitors of the renin-angiotensin system, β receptor antagonists post myocardial infarction (MI), and thienopyridines) as well as agents used primarily for symptom control (eg, calcium channel blockers, nitrates, and other antianginal agents such as ranolazine).[3]

An invasive approach for the treatment of patients is common with more than 1.3 million percutaneous coronary interventions (PCIs) performed in the United States annually, of which $>$ 400,000 are performed for patients with stable angina—and often as the initial therapeutic approach to management.[2] However, the evidence that this approach is superior to optimal medical therapy (OMT) alone in the setting of stable angina remains unclear.

To clarify the evidence that either PCI or OMT would improve clinical outcomes, we conducted a systematic review of prospective, randomized clinical trials in patients with stable angina pectoris. The primary objective of this systematic review and meta-analysis was to determine whether, among patients with stable angina, an initial management strategy of PCI as compared with medical therapy alone reduces all-cause mortal-

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total of 6752 patients. We did not detect differences between PCI vs medical therapy for all-cause mortality (663 events; relative risk [RR], 0.97 [confidence interval (CI), 0.84-1.12]; $I^2 = 0\%$), CV mortality (214 events; RR, 0.91 [CI, 0.70-1.17]; $I^2 = 0\%$), MI (472 events; RR, 1.09 [CI, 0.92-1.29]; $I^2 = 0\%$), or angina relief at the end of follow-up (2016 events; RR, 1.10 [CI, 0.97-1.26]; $I^2 = 85\%$). PCI was not associated with reductions in all-cause or CV mortality, MI, or angina relief. Considering the cost implication and the lack of clear clinical benefit, these findings continue to support existing clinical practice guidelines that medical therapy be considered the most appropriate initial clinical management for patients with stable angina.

données ont été regroupées en utilisant un modèle à effets aléatoires. Dix essais aléatoires prospectifs remplissaient notre critère d'admissibilité et incluaient un total de 6752 patients. Nous n'avons pas détecté de différences entre l'ICP et le traitement médical en ce qui a trait à la mortalité toutes causes confondues (663 événements; risque relatif [RR], 0,97 [intervalle de confiance (IC), 0,84-1,12]; $I^2 = 0\ \%$), la mortalité CV (214 événements; RR, 0,91 [IC, 0,70-1,17]; $I^2 = 0\ \%$), l'IM (472 événements; RR, 1,09 [IC, 0,92-1,29]; $I^2 = 0\ \%$) ou le soulagement de l'angine à la fin du suivi (2016 événements; RR, 1,10 [IC, 0,97-1,26]; $I^2 = 85\ \%$). L'ICP n'a pas été associée aux diminutions de la mortalité toutes causes confondues ou CV, de l'IM ou du soulagement de l'angine. Considérant les conséquences du coût et le manque d'avantages cliniques clairs, ces résultats continuent de soutenir les lignes directrices existantes de la pratique clinique considérant que le traitement médical est la prise en charge clinique initiale des patients ayant une angine stable la plus appropriée.

ity, cardiovascular (CV) mortality, or MI. Our secondary objective was to determine whether a strategy of PCI as compared with medical therapy alone resulted in a lower incidence of recurrent angina at the end of follow-up.

Methods

Protocol

The protocol for trial identification, inclusion and data abstraction was specified a priori and is available upon request. All reviewers were mandated to follow this protocol, and we calculated agreement statistics for the trials included among the reports screened in this systematic review.

Eligibility criteria

We included only randomized controlled trials (RCTs) that assessed the effects of PCI (ie, balloon angioplasty alone, bare metal stent implantation, or drug-eluting stent implantation) compared with medical therapy alone in patients $\geq$ 18 years of age with stable angina. We excluded studies that included patients with unstable patterns of angina (ie, a pattern of accelerating ischemic symptoms including chest pain at rest). We also excluded trials that evaluated PCI vs medical therapy among patients with silent ischemia, unstable angina, or recent MI ($\leq$ 1 month before randomization) as we believed these patients were clinically distinct from patients with stable angina. We did not include studies that solely compared coronary artery bypass grafting (CABG) with medical therapy. We did, however, include trials that randomized patients to CABG as long as the trial randomized patients to 2 arms that allowed us to undertake our comparison of interest (ie, a PCI arm and a medical therapy arm). We excluded 2-arm trials in which conservative treatment was compared against any type of revascularization, including PCI and CABG. We excluded studies that had no relevant event in both the treatment or control groups, because these trials provide no information on the magnitude of the treatment effects.[4] We did not place any restrictions on language.

Trial identification

We used 8 strategies to identify potentially eligible trials. We undertook bibliographic database searches and developed search strategies with the assistance of a research librarian experienced in conducting systematic reviews and meta-analyses. We electronically searched for English and non-English articles using MEDLINE (1950-November 2011), EMBASE (1980-November 2011), and the Cochrane Controlled Trials Register (1993-November 2011). Key words used included angina, stable angina, angina pectoris, percutaneous coronary intervention, stents, and transluminal percutaneous coronary angioplasty. We used the "exploded" search feature in the OVID search software. Additional studies were identified by contacting clinical experts in the field and searching bibliographies and abstracts presented at the American College of Cardiology, the American Heart Association, and the European Society of Cardiology from 1993-present. Finally, our search was supplemented by reviewing the reference lists of all citations that met our final inclusion criteria and by using the "related articles" function on PubMed.

Trial selection

All citations were entered into the EndNote reference management software (2009; Thomson-Reuters, New York, NY) and duplicate records were removed. Two reviewers independently assessed citation titles and abstracts to determine whether the reports fulfilled our eligibility criteria. If either reviewer thought a paper was potentially eligible, the citation was selected to undergo full text evaluation. Two independent reviewers conducted this full text assessment to decide on final inclusion (Fig. 1). Disagreements were resolved by discussion, and a third investigator was consulted for final arbitration of any unresolved disagreements. Cohen's κ was used to quantify agreement between the investigators for final inclusion in the systematic review.

Data abstraction

Information was extracted from included trials on: (1) characteristics of participants including age and mean duration of follow-up, (2) treatment characteristics including medications received and type of PCI performed, (3) inclusion and exclusion criteria of the trials, and (4) the outcomes of interest (all-cause mortality, CV mortality, MI, and the proportion of patients that were angina-free at the end of follow-up). If data were not reported in the primary report we attempted to contact authors and/or obtain data from other references and/or supplemental appendices.

We evaluated the validity of the included trials through assessment of the following factors: concealment of randomization; adequacy of blinding data collectors, and outcome adjudicators; completeness of follow-up; and early/premature ter-

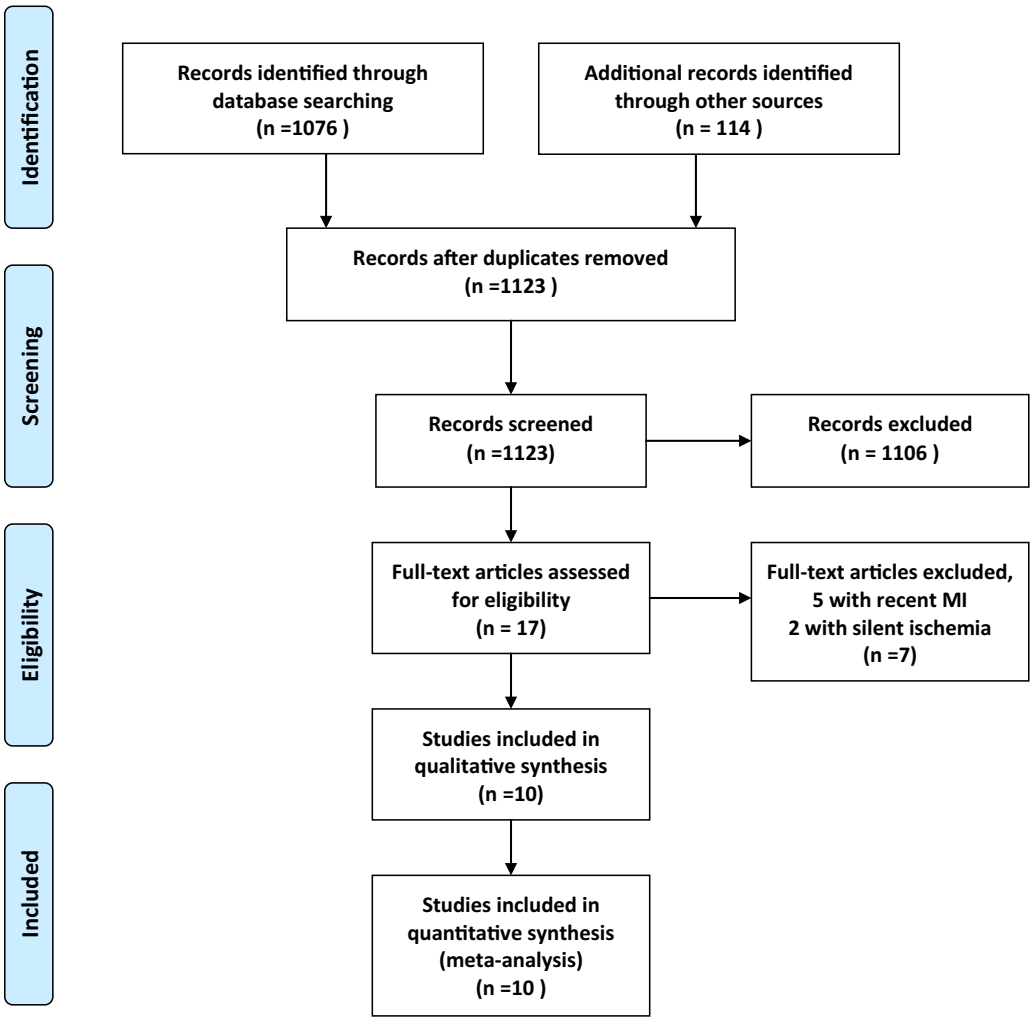

Figure 1. Trial selection search strategy. MI, myocardial infarction.

mination for benefit or harm. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile to summarize the study quality for each of the outcomes of interest.[5]

Statistical analyses

For each RCT, we calculated the relative risk (RR) of the outcomes for patients assigned to PCI compared with medical treatment. For each RR, we determined the 95% confidence intervals. Analyses were conducting according to the intention-to-treat principle. The pooling of results for this meta-analysis was performed using a random-effects/DerSimonian-Laird model. We tested for heterogeneity across trials with the Cochran Q test and also calculated the I^2 statistic to measure consistency among trials.[6] Substantial heterogeneity was defined as any I^2 statistic that exceeded 25%. We hypothesized that effect size may differ according to the methodologic quality of the studies, the number of evidence-based medications patients received, and the duration of follow-up.

Risk of bias across studies

A funnel plot was constructed to graphically illustrate the relationship between standard error and the treatment effect size for all-cause mortality and to assess for publication bias (Fig. 2).

Results

Included trials

Figure 1 summarizes our search strategy. Our trial identification strategies identified 1123 citations. The screening process identified 17 citations that advanced to full text review. A total of 10 trials fulfilled eligibility criteria and were included in this systematic review. Overall eligibility agreement was excellent (κ = 0.91). One eligible trial was published in 2 separate reports; **A**ngioplasty **C**ompared to **M**edicine **E**valuation (ACME)-1 and ACME-2 refers to trials that analyzed patients with single vessel (ACME-1) and double vessel (ACME-2) disease.

Trial characteristics

The 10 included trials are summarized in Table 1. Mean follow-up ranged from 12-80 months. All trials compared PCI with medical therapy. Only 1 trial (**B**ypass **A**ngioplasty **R**evascularization **I**nvestigation in Type **2 D**iabetes [BARI 2D][19]) used a 2 × 2 factorial design assigning patients with both type 2 diabetes and CAD to undergo either revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy.[19] We excluded the CABG vs OMT cohort from BARI 2D.

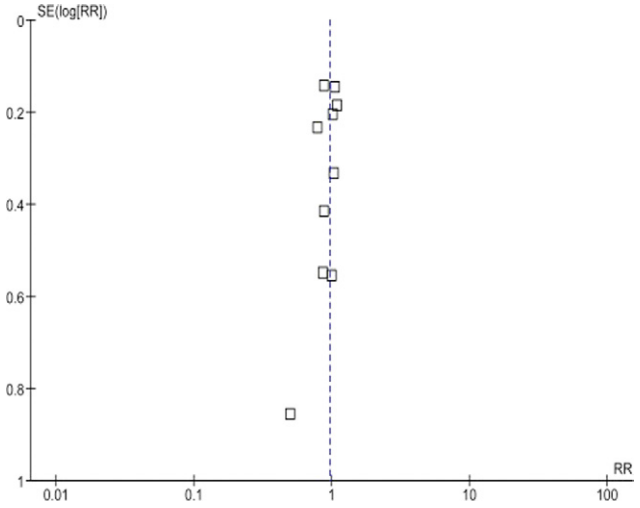

Figure 2. Funnel plot comparing standard error (SE) and relative risk (RR) for all-cause mortality.

Study participants ranged in age from 58 to 80 years of age. Women were underrepresented in many of the trials. The ACME trial[7,8] enrolled no women, owing to the fact that this was a Veterans Affairs-based trial while the **M**edicine, **A**ngioplasty, or **S**urgery **S**tudy (MASS)[9,10,16] and **T**rial of **I**nvasive vs **M**edical Therapy in **E**lderly Patients (TIME)[15] trials enrolled approximately 40% of subjects who were women. Patient ethnicity was not fully reported in the included trials. The majority of patients had Canadian Cardiovascular Society (CCS) class I-II stable angina at baseline. In the TIME trial, the majority of patients did not have an MI however the exclusion criteria mention that patients were excluded if they had an MI $<$ 10 days from randomization. It is possible that patients were included who had MIs between 10 and 30 days from randomization. We therefore performed a separate sensitivity analysis removing the contribution of the TIME trial to assess its effect on all-cause mortality, CV mortality, and the incidence of MI.

The type of PCI varied considerably among trials, largely as a function of the long timeline associated with the pooling of these results, where older studies (eg, ACME) dated back to the mid to late 1980s. Accordingly, the use of stents in PCI ranged from 0% in the ACME trial[7,8] to 100% in the study from Hambrecht et al.[14] Medical therapy also varied considerably. While the majority of trials used aspirin, the use of β-blockers, inhibitors of the renin-angiotensin system, and statins varied considerably. **C**linical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive Dru**g** **E**valuation (COURAGE)[17] and BARI 2D[19] employed what is widely regarded today as OMT with $>$ 80% of patients in both the PCI and medical therapy arms receiving aspirin, β-blockers, and statins. We obtained baseline medication use from all original reports. Baseline medication use is reported in Table 2.

Risk of bias within studies

We used the GRADE evidence profile to assess study quality for each of the outcomes of interest.[5] All studies had limitations regarding the quality of evidence using this classification scheme. All the trials included were unblinded. Both the patients and their health care provider were aware of the treatment arm to which they were randomized. No sham PCI procedure was performed in any of the trials. Although there are practical limitations of complete blinding and sham controls in this situation, blinding was nonetheless reported as a methodologic limitation for the purpose of this review. This is because angina is reported by patients and potentially influenced by knowledge of the intervention received as physicians could potentially differentially apply anti-ischemic medications based on knowledge of the assigned intervention. Concealment was absent, inadequate, or not reported in 4/10 trials included, notably: ACME,[7,8] MASS,[9,10] Bech et al.,[11] and MASS-II.[16] With respect to angina relief, we also found incomplete blinding in all of the trials and inadequate concealment in 4/7 trials (ACME,[7,8] MASS,[9,10] Bech et al.,[11] and MASS-II[16]). Study quality is summarized in Table 3. The risk of bias is summarized in Table 4 as the GRADE evidence profile.

Effect of PCI vs medical therapy on clinical outcomes

Ten studies with 6752 patients reported all-cause mortality. None of the individual trials showed significant differences between PCI or medical therapy. The pooled analysis revealed that there were a total of 663 deaths, with 326 deaths in the PCI group and 337 deaths in the medical therapy group with a RR = 0.97 (confidence interval [CI], 0.84-1.12) (Fig. 3). There was no significant statistical herterogeneity among the trials for all-cause mortality ($I^2 = 0$; $P = 0.97$).

Six studies representing 4674 patients reported CV mortality. None of the individual trials reported significant differences between PCI or medical therapy. There were a total of 214 CV deaths (102 in the PCI group and 112 in the medical therapy group with a RR = 0.91 (CI, 0.7-1.17) (Fig. 4). There was no significant statistical herterogeneity for CV mortality ($I^2 = 0$; $P = 0.99$).

Nine studies representing 5147 patients reported MI as an outcome of interest after randomization. Again, none of the trials reported significant differences between PCI or medical therapy. There were a total of 472 MIs (248 in the PCI group and 224 in the medical therapy group with an RR = 1.09 (CI, 0.92-1.29) (Fig. 5). There was no significant statistical herterogeneity for MI ($I^2 = 0$; $P = 0.46$).

Seven studies representing 2846 patients reported angina relief at the end of follow-up. ACME[7,8] and MASS[9,10,16] reported significantly more patients who remained angina-free at the end of follow-up with PCI as compared with medical therapy. The remaining studies including the COURAGE trial[17] found no significant difference between the proportion of patients remaining angina-free at the end of follow-up with either a strategy of PCI or medical therapy. The overall pooled estimate of effect reported no significant differences between PCI or medical therapy for angina relief (RR, 1.10; CI, 0.97-1.26) (Fig. 6). There was, however, significant statistical herterogeneity for this outcome as evidenced by point estimates on either side of unity and nonoverlapping CIs ($I^2 = 85\%$; $P <$ 0.00001).

Overall, there was no significant difference in all-cause mortality, CV mortality, or MI when either an initial PCI or medical strategy was adopted. Because some of the patients in the TIME trial may have had an MI 10-30 days before randomization, this was further assessed in a sensitivity analysis. Removal of the TIME trial from the forest plots did not affect the overall conclusion for all-cause mortality, CV mortality, and incidence of MI. For the secondary outcome of angina relief at

Table 1. Study characteristics

Trial	Recruitment years	Follow-up (mo)	Mean age (y)	Stent use (%)	Inclusion criteria	Exclusion criteria	Outcome	Sponsorship
ACME (1 and 2)[7,8] (N = 328)	1987-1990	60	60	0	Stable angina with significantly positive stress test or MI within 3 months, stenosis > 70% in the proximal 2/3 of a single vessel	Unstable angina refractory to medication, previous PCI, left main artery stenosis > 50%, > 70% in more than 1 coronary artery, EF < 30%	Death, MI, recurrent cardiac hospitalization, need for revascularization	University/national sponsorship
MASS[9,10] (N = 144)	1988-1991	60	65	0	Stable angina, normal EF, inducible ischemia; stenosis > 80% before first diagonal branch < 12 mm in length	Previous revascularization, Q-wave MI, LV dysfunction, total occlusion or tortuous, calcified lesions, > 50% stenosis of left main	Cardiac death, MI, refractory angina requiring hospitalization	University/national sponsorship
Bech et al.[11] (N = 181)	1997-1998	24	61	46	≥ CCS class I angina, no reversible ischemia, stenosis > 50% in a native coronary artery	Total occlusion, Q-wave MI or unstable angina, small target vessel < 2.5 mm diameter	Total mortality, MI, revascularization, procedure-related complication	Sponsorship not reported
RITA-2[12,13] (N = 1018)	1992-1996	84	58	9	Stable or unstable angina, last episode ≥ 7 days before randomization, single or multivessel disease, stenosis in at least 1 artery, > 50% stenosis in 2 views or > 70% stenosis in 1 view	Left main disease, previous revascularization, recent (< 7 days) acute coronary syndrome	All-cause death or MI	Partial industry sponsorship
Hambrecht et al.[14] (N = 101)	1997-2001	12	60	100	CCS class I-III angina with documented ischemia during stress test, 1 native coronary artery stenosis > 75%	Age > 70 y, acute coronary syndrome, recent MI (< 2 mo), EF < 40%, revascularization within past 12 mo, 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	University/national sponsorship
TIME[15] (N = 301)	1996-2000	48	80	86	Age < 75 y with chronic CCS class 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)	University/national sponsorship
MASS-2[16] (N = 408)	1995-2000	60	60	72	Documented ischemia (stress testing or CCS class II or III angina), proximal multivessel coronary stenosis > 70%	Age > 80 y, 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	University/national sponsorship
COURAGE[17] (N = 2287)	1991-2004	54	61	94	CCS I, CCS II angina, or initial CCS IV angina stabilized medically, stable post-MI, 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 testing	Age > 69 y, persistent CCS IV angina, markedly positive stress test, refractory heart failure or cardiogenic shock, EF < 30%, revascularization within 6 mo, unprotected left main artery stenosis > 50%	Composite of all-cause mortality or MI	Partial industry sponsorship
JSAP[18] (N = 379)	2002-2004	40	64	76	Age 30-75 y with stable low risk CAD with 1 or 2 vessel disease ≥ 60%. Must have demonstrable ischemia by stress ECG and/or chest pain	Three-vessel disease, left main disease, chronic total obstruction, ACS (MI/unstable angina), LVEF < 50%, lesions not amenable to PCI, Cr > 1.5 mg/dL, previous CABG with saphenous vein disease	All-cause mortality, ACS, CVA, emergency hospitalization	University/national sponsorship
BARI-2D[19] (N = 1605)	2001-2005	63	62	91	Diagnosis of DM-2 and CAD defined as ≥ 50% stenosis with inducible ischemia or ≥ 70% stenosis and classic angina	Require immediate revascularization or have left main disease, Cr > 2 mg/dL, HbA1c > 13%, class III, IV heart failure, hepatic dysfunction, undergone PCI/CABG within the previous 12 months	All-cause mortality	Partial industry sponsorship

ACME, **A**ngioplasty **C**ompared to **M**edicine **E**valuation; ACS, acute coronary syndromes; BARI-2D, **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation in Type **2** **D**iabetes; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COURAGE, **C**linical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive Dru**g** **E**valuation; Cr, creatinine; CVA, cerebrovascular accident; DM-2, type 2 diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; HbA1c, hemoglobin A1c; JSAP, **J**apanese **S**tudy of Stable **A**ngina **P**ectoris; LV, left ventricular; LVEF, LV ejection fraction; MASS, **M**edicine, **A**ngioplasty, or **S**urgery **S**tudy; MI, myocardial infarction; PCI, percutaneous coronary intervention; RITA, **R**andomized **I**ntervention **T**reatment of **A**ngina; TIME, **T**rial of **I**nvasive vs **M**edical Therapy in **E**lderly Patients.

Table 2. Baseline medication use in PCI and medical therapy groups

	Aspirin (%)		β-Blockers (%)		ACE inhibitors plus ARB (%)		Statins/lipid lowering agents (%)		Nitrates (%)		CCB (%)	
Trial	PCI	Medical therapy	PCI	Medical therapy	PCI	Medical therapy	PCI	Medical therapy	PCI	Medical therapy	PCI	Medical therapy
ACME 1 and 2 (N = 328)	91	83	39	42	NA	NA	NA	NA	48	61	78	73
MASS (N = 144)	75	78	52	46	30	25	42	36	NA	NA	NA	NA
Bech et al.[11] (N = 181)	92	92	62	71	NA	NA	37	37	53	56	47	43
RITA-2 (N = 1018)	87	87	68	65	9	11	13	12	46	40	47	53
Hambrecht et al.[14] (N = 101)	98	98	86	88	88	74	80	72	0	0	0	0
TIME (N = 301)	85	82	82	72	23	35	25	22	76	76	51	49
MASS-2 (N = 408)	80	80	61	68	30	29	73	68	41	73	30	61
COURAGE (N = 2287)	96	95	85	89	62	65	94	97	62	72	40	43
JSAP (N = 379)	92	91	44	52	41	39	55	52	51	57	57	59
BARI-2D (N = 1605)	93	94	83	88	91	92	95	95	16	26	0	0

ACE, angiotensin-converting enzyme; ACME, **A**ngioplasty **C**ompared to **M**edicine **E**valuation; ARB, angiotensin-receptor blocker; BARI-2D, **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation in Type **2** **D**iabetes; CCB, calcium channel blocker; COURAGE, **C**linical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive Dru**g** **E**valuation; JSAP, **J**apanese **S**tudy of Stable **A**ngina **P**ectoris; MASS, **M**edicine, **A**ngioplasty, or **S**urgery **S**tudy; NA, not applicable; PCI, percutaneous coronary intervention; RITA, **R**andomized **I**ntervention **T**reatment of **A**ngina; TIME, **T**rial of **I**nvasive vs **M**edical Therapy in **E**lderly Patients.

the end of follow-up, we could not discern a clear benefit for PCI over medical therapy; however, we assigned this finding a quality of evidence rating of "low" based on incomplete blinding, inadequate concealment, and significant statistical heterogeneity among the included trials. The evidence profiles for all the outcomes of interest are reported in Table 5.

Risk of publication bias across studies

The funnel plot (Fig. 2) of the standard error of the log of RR against RR for all-cause mortality with PCI vs medical therapy did not identify any significant publication bias.

Discussion

The principal finding of our meta-analysis of RCTs comparing PCI with medical therapy was that there was no significant difference in all-cause mortality, CV mortality, or MI between the 2 assigned initial management strategies. While clearly there was methodologic variability among trials because of the evolution of PCI over the long time horizon during which these trials were conducted and reported, it is noteworthy that the earlier trials performed in the early 1990s (ACME[7,8]) and late 1990s (MASS[9,10,16]) had similar point estimates as compared with more contemporary trials such as COURAGE[17] and BARI 2D.[19] This is reflected in the $I^2 = 0$ for these outcomes.

For the outcome of angina relief at the end of follow-up, our meta-analysis also found no significant difference with respect to a strategy of PCI vs medical therapy. This is consistent with previous studies. In fact, 66% of PCI patients in the COURAGE trial were angina-free at 1 year vs 58% for OMT and its statistical superiority lasted for only 3 years, after which restenosis or atherosclerotic progression very likely intervened.[20] Because of methodologic limitations in our meta-analysis including incomplete blinding and inadequate concealment combined with significant statistical heterogeneity ($I^2 = 85\%$), our confidence in this estimate is "low" by comparison to the other "hard'" endpoints of all-cause or CV mortality and nonfatal MI. This suggests that further studies may change our point estimate of effect.

The optimal management of stable angina continues to remain an area of continuing controversy. Proponents of an initial management strategy of "PCI first" argue that improved blood flow leads to reduced ischemic substrate and improved overall prognosis.[21] Opponents claim that patients with stable coronary artery disease have coronary plaques that are less likely to result in an acute coronary syndrome,[22] and therefore, intervening focally on a coronary lesion with PCI is unlikely to alter a patient's overall prognosis. Hence, an initial management strategy of "OMT first" is advocated by many clinicians, and is becoming in-

Table 3. Study quality assessment

Trial	Randomized	Randomization description	Double blinded	Blinding description	Withdrawal descriptions	Allocation concealment
ACME 1 and 2	Yes	Yes	No	NA	Yes	Unknown
MASS	Yes	Yes	No	NA	Yes	Unknown
Bech et al.[11]	Yes	Yes	No	NA	Yes	Unknown
RITA-2	Yes	Yes	No	NA	Yes	Yes
Hambrecht et al.[14]	Yes	Yes	No	NA	Yes	Yes
TIME	Yes	Yes	No	NA	Yes	Yes
MASS-2	Yes	Yes	No	NA	Yes	Unknown
COURAGE	Yes	Yes	No	NA	Yes	Yes
JSAP	Yes	Yes	No	NA	Yes	Yes
BARI-2D	Yes	Yes	No	NA	Yes	Yes

ACME, **A**ngioplasty **C**ompared to **M**edicine **E**valuation; BARI-2D, **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation in Type **2** **D**iabetes; COURAGE, **C**linical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive Dru**g** **E**valuation; JSAP, **J**apanese **S**tudy of Stable **A**ngina **P**ectoris; MASS, **M**edicine, **A**ngioplasty, or **S**urgery **S**tudy; NA, not applicable; RITA, **R**andomized **I**ntervention **T**reatment of **A**ngina; TIME, **T**rial of **I**nvasive vs **M**edical Therapy in **E**lderly Patients.

Table 4. GRADE evidence profile

Quality assessment							Summary of findings					
							Patients, n		Effect			
Studies, n	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	Medical therapy alone	RR (95% CI)	Absolute	Quality	Importance
All-cause mortality (follow-up mean 4.4 y) 10	Randomized trials	Serious*	No serious inconsistency	No serious indirectness	No serious imprecision	None	326/3375 (9.7%)	337/3377 (10%)	RR, 0.97 (0.84-1.12)	3 fewer per 1000 (from 16 fewer to 12 more)	High	Critical
Cardiovascular mortality (follow-up mean 4.1 y) 7	Randomized trials	Serious†	No serious inconsistency	No serious indirectness	None	None	102/2339 (4.4%)	112/2335 (4.8%)	RR, 0.91 (0.7-1.17)	4 fewer per 1000 (from 14 fewer to 8 more)	High	Critical
Myocardial infarction (follow-up mean 4.3 y) 9	Randomized trials	Serious‡	No serious inconsistency	No serious indirectness	None	None	248/2577 (9.6%)	224/2570 (8.7%)	RR, 1.09 (0.92-1.29)	8 more per 1000 (from 7 fewer to 25 more)	High	Important
Angina relief (follow-up mean 4.6 y) 7	Randomized trials	Serious§	Serious¶	No serious indirectness	None	None	1054/1425 (74%)	962/1421 (67.7%)	RR, 1.10 (0.97 to 1.26)	68 more per 1000 (from 20 fewer to 176 more)	Low	Important

ACME, **A**ngioplasty **C**ompared to **M**edicine **E**valuation; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MASS, **M**edicine, **A**ngioplasty, or **S**urgery **S**tudy; PCI, percutaneous coronary intervention; RR, relative risk.

* Patients and providers were not blinded in any of the included trials. Allocation concealment not reported in 3/10 trials (ACME, Bech et al.,[11] and MASS-II).

† Patients and providers were not blinded in any of the included trials. Allocation concealment not reported in 3/7 trials (Bech et al.,[11] MASS-I, MASS-II).

‡ Patients and providers were not blinded in any of the included trials. Allocation concealment not reported 4/9 trials (ACME, MASS, Bech et al.,[11] and MASS-II).

§ Patients and providers were not blinded in any of the included trials. Allocation concealment not reported in 4/7 trials (ACME, MASS-I, Bech et al.,[11] MASS-II).

¶ Significant heterogeneity noted $I^2 = 85\%$; $P < 0.00001$.

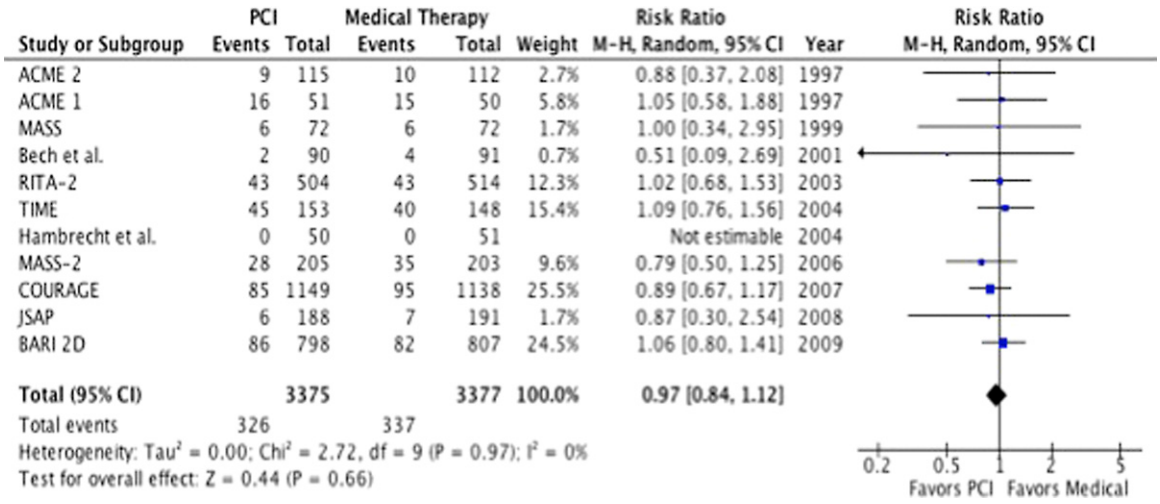

Figure 3. All-cause mortality. ACME, Angioplasty Compared to Medicine Evaluation; BARI-2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Study of Stable Angina Pectoris; M-H, Mantel-Haenszel; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; TIME, Trial of Invasive vs Medical Therapy in Elderly Patients.

creasingly embraced by third party payers and insurance companies that seek to minimize procedures that do not meet "appropriate use criteria."

While contemporary randomized trials such as the COURAGE[17] and BARI 2D[19] demonstrate that PCI plus OMT does not reduce the risk of death or MI in patients with stable angina compared with OMT alone, more criticisms and more recent studies are again challenging this conclusion that PCI should not be viewed as being ineffective in all patients with stable ischemic heart disease. The COURAGE trial nuclear substudy of 314 patients showed that PCI reduced moderate to severe ischemia better than OMT, but the data were inconclusive as to whether the ischemia reduction with PCI resulted in improved clinical event reduction. In particular, among 105 patients with ≥ 10% ischemia in the this nuclear substudy, those who received PCI were more likely to experience significant ischemia reduction compared with OMT alone (78% vs 52%; $P = 0.007$)—this translated to a lower unadjusted risk for death or MI,[23] but this was a relatively small subset of patients and the observation is likely highly underpowered.

Previously, Hachamovitch et al., in a 2-year observational study of 10,627 patients with moderate-to-severe ischemia who were evaluated on myocardial perfusion imaging, demonstrated that patients undergoing revascularization had a survival benefit over those who were not revascularized.[18]

In a subsequent trial, the **J**apanese **S**tudy of Stable **A**ngina **P**ectoris (JSAP) among patients with CAD showed that a combined strategy of PCI and OMT reduced the incidence of acute coronary syndromes more effectively than OMT alone,[24] but these were minimally symptomatic patients who did not receive robust medical therapy.

The conclusions of our meta-analysis vary significantly from these recent studies including recently published meta-analyses. A meta-analysis by Schomig et al. suggested that a PCI-based invasive strategy compared with medical therapy alone would improve all-cause mortality (odds ratio [OR], 0.8; CI, 0.64-0.99) and cardiovascular mortality (OR, 0.74; CI, 0.51-1.06).[21] This meta-analysis did not detect a difference in the incidence of MI (OR, 0.90; CI, 0.66-1.23) with PCI vs medical therapy. The review from Schomig et al. included 17 trials with 7513 patients, which includes more data than our review. This meta-analysis however, had a high degree of clinical heterogeneity. Of the studies that were included, 5 studies (Dakik et al.,[25] **Dan**ish Trial in **A**cute **M**yocardial **I**nfarction [DANAMI],[26] **Swi**ss **I**nterventional **S**tudy on

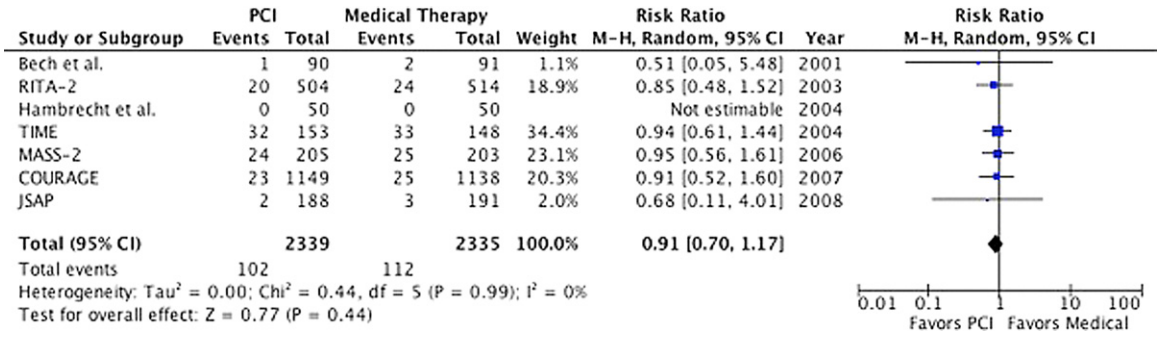

Figure 4. Cardiovascular mortality. CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Study of Stable Angina Pectoris; M-H, Mantel-Haenszel; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; TIME, Trial of Invasive vs Medical Therapy in Elderly Patients.

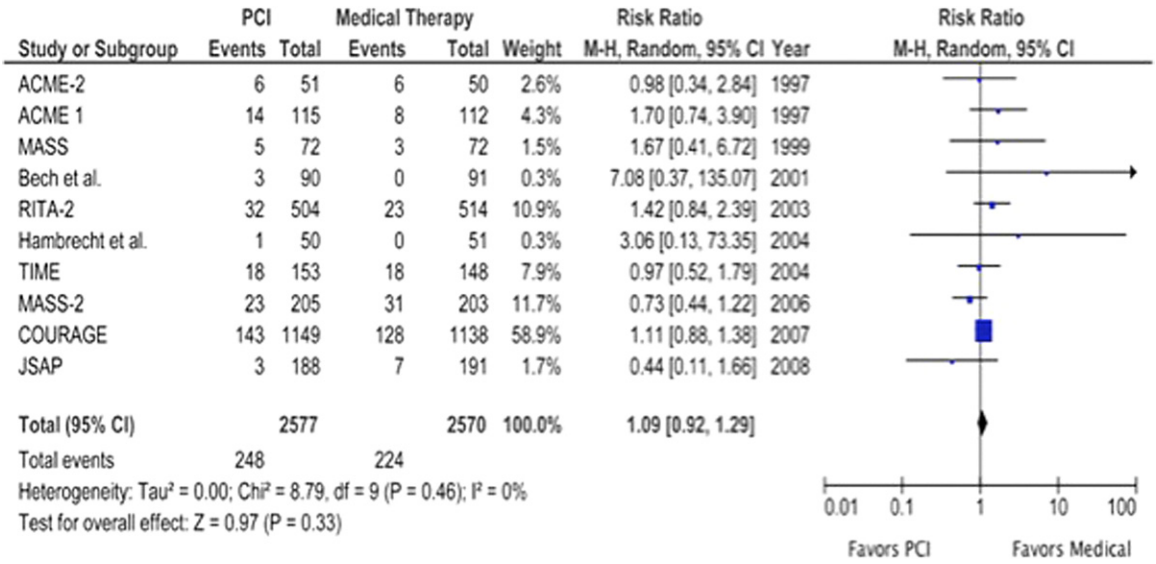

Figure 5. Incidence of myocardial infarction. ACME, Angioplasty Compared to Medicine Evaluation; BARI-2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; JSAP, Japanese Study of Stable Angina Pectoris; M-H, Mantel-Haenszel; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomized Intervention Treatment of Angina; TIME, Trial of Invasive vs Medical Therapy in Elderly Patients.

Silent **I**schemia Type **II** [SWISSI-II],[27] **A**denosine **S**estamibi **P**ost-**I**nfa**r**ction **E**valuation [INSPIRE],[28] and **A**rbeitsgemeinschaft **L**eitende **K**ardiologische **K**rankenhausarzte [ALKK][29]) were of patients with recent MIs, and 2 studies (**A**symptomatic **C**ardiac **I**schemia **P**ilot [ACIP],[30] and Sievers[31]), evaluated silent ischemia. We believe that these patients are substantially different from patients with stable angina and were therefore excluded from our meta-analysis.

The meta-analysis from Wijeysundera et al. is the first review to evaluate the effect of PCI compared with medical therapy for angina relief at the end of follow-up.[32] The authors concluded that PCI was associated with greater freedom from angina compared with medical therapy. This meta-analysis included 14 trials with 7818 patients. Of the trials that were included, **T**reatment **o**f **P**ost-Thrombolytic **S**tenoses (TOPS),[33] Dakik et al.,[25] SWISSI-II,[27] INSPIRE,[28] ALKK,[29] **De**sobstruction **Co**ronaire en **P**ost-**I**nfarctus (DECOPI),[34] and **O**ccluded **A**rtery **T**rial (OAT)[12] were of patients with recent MIs that were also excluded from our analysis.

It is likely that the clinical heterogeneity in this meta-analysis explains their different results than our meta-analysis. The authors did note that this benefit of PCI was attenuated in more contemporary trials.

Finally, our findings are consistent with a recent meta-analysis by Stergiopoulos and Brown.[35] Our systematic reviews differed in that Stergioupoulos and Brown only included trials that had > 50% stent use in the PCI arm and they included trials evaluating asymptomatic patients with ischemia and patients with recent MIs. Based on these differences, our meta-analysis represents a broader group of symptomatic patients with truly stable disease.

Limitations

Like all meta-analyses, our systematic review and meta-analysis should be interpreted within the context of several limitations. First, the moderate to low quality of evidence attributed to methodologic issues informs us that further research may change our

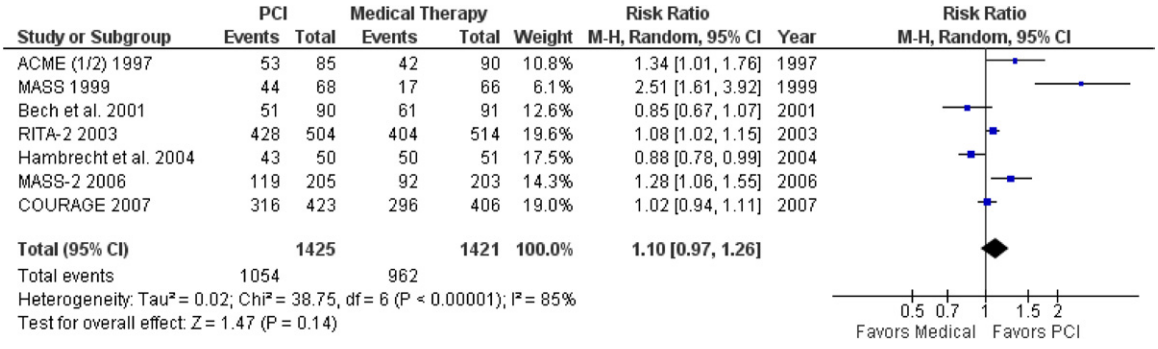

Figure 6. Angina relief. ACME, Angioplasty Compared to Medicine Evaluation; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; MASS, Medicine, Angioplasty, or Surgery Study; M-H, Mantel-Haenszel; RITA, Randomized Intervention Treatment of Angina.

Table 5. GRADE evidence profile for outcomes of interest

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Participants, n (studies, n)	Quality of the evidence (GRADE)†
	Assumed risk	Corresponding risk			
	Medical therapy alone	PCI			
All-cause mortality; follow-up mean 4.4 y	100 per 1000	97per1000 (84-112)	RR,0.97 (0.84-1.12)	6752 (10)	High
Cardiovascular mortality; follow-up mean 4.1 y	48 per 1000	44per1000 (34-56)	RR,0.91 (0.7-1.17)	4674 (7)	High
Myocardial infarction; follow-up mean 4.3 y	87 per 1000	95per1000 (80-112)	RR,1.09 (0.92-1.29)	5147 (9)	High
Angina relief; follow-up mean 4.6 y	677 per 1000	745per1000 (657-853)	RR,1.10 (0.97-1.26)	2846 (7)	Low‡

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PCI, percutaneous coronary intervention; RR, relative risk.

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

† GRADE Working Group grades of evidence: High quality, further research is very unlikely to change our confidence in the estimate of effect; Moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality, we are very uncertain about the estimate.

‡ Significant heterogeneity noted.

estimate of effect. Furthermore, we had incomplete information on medication use rates, dosages, or long-term adherence.

Because the trials included in this systematic review enrolled patients from 1992 to 2009, there are valid concerns that these studies do not reflect modern practice in managing stable angina. For instance, the **R**andomized **I**ntervention **T**reatment of **A**ngina (RITA)-2 investigators found an increased frequency of death or MI from procedure-related complications (6.3% in the angioplasty arm vs 3.3% in the medical arm).[36] Also, coronary stent use was limited to 9% of PCI patients and < 20% of enrolled patients were prescribed an inhibitor of the renin-angiotensin system or a statin.[36] The safety of PCI has likely improved substantially since then with more frequent use of stents, which have markedly reduced periprocedural complications. Also medical therapy has significantly improved in the interim as well with the majority of patients receiving angiotensin-converting enzyme inhibitors and statin medications.

Implications for future research

Our findings do not shed definitive light on whether PCI is superior to medical therapy for long-term angina relief, which would likely require a modern prospective trial using truly OMT compared with optimal PCI treatments and 1 that would use several well-validated quality of life instruments. Because many observational studies including the COURAGE nuclear substudy[37] imply that patients with significant ischemic burden benefit from PCI, this important scientific question remains unanswered, but will be addressed prospectively in a large National Institutes of Health-funded, multicentre, multinational, prospective trial in 8000 patients with moderate to severe inducible ischemia who will be randomized to OMT with or without contemporary revascularization in order to determine if patients with a high ischemic burden may benefit from either PCI or CABG.[13]

Conclusions

In summary, this meta-analysis has shown that there is no difference with respect to all-cause mortality, CV mortality, or the incidence of MI with an initial management strategy of medical therapy alone as compared with PCI plus medical therapy. Our findings also suggest that either strategy is equivalent with respect to angina relief at the end of follow-up, although the confidence of this finding is less certain. Our results continue to reinforce existing clinical practice guidelines that the initial approach to patients with stable angina should be medical therapy. If patients have recurrent angina despite intensification of medical therapy, it is reasonable to proceed with PCI in those for whom medical therapy has ostensibly failed. Finally, if patients believe that their degree of angina or quality of life is sufficiently compromised despite medical therapy, it is appropriate to consider PCI solely for symptom relief, although it remains unclear whether PCI is a durable treatment for angina beyond a finite time period (eg, 1-3 years), as compared with OMT.[38]

Disclosures

The authors have no conflicts of interest to disclose.

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