

## Original Investigation

# Percutaneous Coronary Intervention Outcomes in Patients With Stable Obstructive Coronary Artery Disease and Myocardial Ischemia

## A Collaborative Meta-analysis of Contemporary Randomized Clinical Trials

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**IMPORTANCE** Myocardial ischemia in patients with stable coronary artery disease (CAD) has been repeatedly associated with impaired survival. However, it is unclear if revascularization with percutaneous coronary intervention (PCI) to relieve ischemia improves outcomes compared with medical therapy (MT).

**OBJECTIVE** The objective of this study was to compare the effect of PCI and MT with MT alone exclusively in patients with stable CAD and objectively documented myocardial ischemia on clinical outcomes.

**DATA SOURCES** MEDLINE, Cochrane, and PubMed databases from 1970 to November 2012. Unpublished data were obtained from investigators.

**STUDY SELECTION** Randomized clinical trials of PCI and MT vs MT alone for stable coronary artery disease in which stents and statins were used in more than 50% of patients.

**DATA EXTRACTION** For studies in which myocardial ischemia diagnosed by stress testing or fractional flow reserve was required for enrollment, descriptive and quantitative data were extracted from the published report. For studies in which myocardial ischemia was not a requirement for enrollment, authors provided data for only those patients with ischemia determined by stress testing prior to randomization. The outcomes analyzed included death from any cause, nonfatal myocardial infarction (MI), unplanned revascularization, and angina. Summary odds ratios (ORs) were obtained using a random-effects model. Heterogeneity was assessed using the  $Q$  statistic and  $I^2$ .

**RESULTS** In 5 trials enrolling 5286 patients, myocardial ischemia was diagnosed in 4064 patients by exercise stress testing, nuclear or echocardiographic stress imaging, or fractional flow reserve. Follow-up ranged from 231 days to 5 years (median, 5 years). The respective event rates for PCI with MT vs MT alone for death were 6.5% and 7.3% (OR, 0.90 [95% CI, 0.71-1.16]); for nonfatal MI, 9.2% and 7.6% (OR, 1.24 [95% CI, 0.99-1.56]); for unplanned revascularization, 18.3% and 28.4% (OR, 0.64 [95% CI, 0.35-1.17]); and for angina, 20.3% and 23.3% (OR, 0.91 [95% CI, 0.57-1.44]).

**CONCLUSIONS AND RELEVANCE** In patients with stable CAD and objectively documented myocardial ischemia, PCI with MT was not associated with a reduction in death, nonfatal MI, unplanned revascularization, or angina compared with MT alone.

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← Editor's Note page 231

← Related article page 223

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Worldwide, coronary artery disease (CAD) is the leading cause of death and will continue to be at least through the year 2030.<sup>1</sup> Approximately 1 in 30 patients with stable CAD experiences cardiovascular death or myocardial infarction (MI) each year.<sup>2</sup> The increasing global prevalence of CAD<sup>3</sup> coupled with these high event rates underscores the need to identify and intervene in patients at highest risk for these adverse clinical outcomes. Because an ischemic response on stress testing identifies an increased risk of death or MI in patients with CAD, the presence of myocardial ischemia is commonly used to select patients with stable CAD for elective coronary revascularization even in the absence of limiting symptoms under the assumption that since ischemia confers adverse risk,<sup>4-7</sup> reducing ischemia by revascularization will reduce risk.<sup>8,9</sup>

More recently, fractional flow reserve (FFR) has emerged as an invasive technique performed at the time of coronary angiography to detect coronary stenoses of sufficient hemodynamic severity to induce myocardial ischemia.<sup>8</sup> *Fractional flow reserve* is defined as the maximal blood flow to the myocardium in the presence of a stenosis in the supplying coronary artery divided by the theoretical normal maximal flow in the same distribution. This index represents the fraction of the normal maximal myocardial flow that can be achieved despite the coronary stenosis. The normal value of the index is 1.0, regardless of the patient or the specific vessel studied. The positive predictive value of an FFR of less than approximately 0.75 for identifying coronary stenoses associated with reversible myocardial ischemia is 100%<sup>10</sup> and is therefore used to select lesions for percutaneous coronary intervention (PCI) with the goal of reducing ischemia and improving outcomes.<sup>9</sup>

In support of the strategy of ischemia-guided revascularization, a large observational study of patients in the 1990s suggested that revascularization in patients with evidence of at least moderate ischemia (>10% of the myocardium) was associated with fewer cardiac deaths than treatment with medical therapy (MT) alone.<sup>4</sup> Conversely, 2 post hoc studies of patients enrolled in the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial with either mild or moderate to severe ischemia at baseline failed to demonstrate a reduction in death or MI in patients treated with PCI compared with those who received MT.<sup>11,12</sup>

Given the equipoise surrounding this issue, we performed a systematic review and collaborative meta-analysis of contemporary randomized clinical trials that compared PCI and MT with initial MT alone in patients with stable obstructive CAD and objectively documented ischemia.

## Methods

### Search Strategy

A systematic search of published studies in any language in MEDLINE, Cochrane, and PubMed from 1970 to November 2012 was performed independently by 2 of us (K.S. and D.L.B.). Search terms included *stent*, *medical therapy*, *stable angina*, *coronary artery disease*, and combinations of these terms. A

filter for randomized clinical trials was used. Additionally, bibliographies of retrieved articles and prior reviews on the subject were searched for other relevant studies.

### Inclusion Criteria

For inclusion, studies were required to be prospective, randomized trials of PCI plus MT vs MT alone in patients with stable CAD with the individual outcomes of death and nonfatal MI reported. Additionally, to reflect contemporary interventional and medical practice, inclusion required stent implantation in at least 50% of PCI procedures and statin medications in at least 50% of patients in both PCI and MT arms. Finally, myocardial ischemia or abnormal FFR had to be documented in some or all patients prior to randomization. For studies in which MT was compared with separate arms of PCI or coronary artery bypass graft (CABG) surgery,<sup>13,14</sup> only the comparisons of MT vs PCI were extracted. Studies of stable patients following a completed MI were excluded as were trials in which MT was compared with any form of revascularization (PCI or CABG).

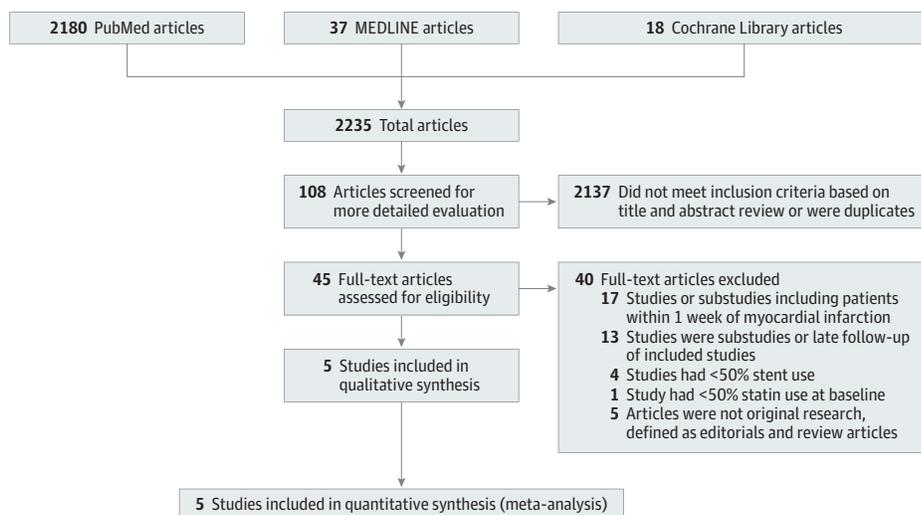
### Data Extraction

For studies in which all patients had either myocardial ischemia on stress testing or an abnormal FFR,<sup>15,16</sup> patient characteristics, study design, and outcomes were systematically reviewed and recorded independently by 2 of us (K.S. and D.L.B.). For studies in which not all patients were required to have ischemia on stress testing,<sup>13,14,17</sup> the primary authors were contacted and provided data on the subset of patients with ischemia at the time of randomization. For a study in which some end points of interest (all-cause mortality, angina) were not reported,<sup>15</sup> the primary authors were contacted and provided the data. Study quality was evaluated according to the criteria of Jadad et al,<sup>18</sup> which included ascertainment of randomization, blinding of the patient and investigator to treatment allocation, and an account of the patients who withdrew.

### Outcomes

The following clinical outcomes were analyzed: death from any cause, nonfatal MI, unplanned revascularization (PCI or CABG), and angina. For each outcome, we used data from the longest follow-up available for that particular outcome to a maximum follow-up of 5 years. End point definitions were those used in the individual trials. The definition of nonfatal MI varied and became more precise in the more recent studies. In general, the diagnosis of nonfatal MI required appropriate symptoms, biomarker elevation, and/or electrocardiographic changes. Nonfatal postprocedural MI, when identified, was included as a nonfatal MI event. Troponin screening for post-procedure MI was used in 2 studies.<sup>14,17</sup> Unplanned revascularization included any PCI or CABG excluding the PCI mandated by initial randomization and could occur in participants initially assigned to either PCI or MT arms. In each study, revascularization decisions were made by the treating physician and not mandated by the study protocols. The definition of angina was that used in the individual trials and included recurrent or persistent angina during follow-up.

Figure 1. Study Selection



Flow diagram depicts study selection for inclusion in the meta-analysis according to the PRISMA statement for reporting systematic reviews and meta-analyses.<sup>19</sup>

### Statistical Analysis

Because individual patient-level data from each trial were not available, a meta-analysis of summary statistics from individual trials was performed using Comprehensive Meta Analysis software, version 2 (Biostat Inc). Data were analyzed according to the intention-to-treat principle. For trials with no events in either treatment group,<sup>15</sup> a nominal amount (0.5 cases) was added to the results for both groups. The presence of statistically significant heterogeneity was assessed by the *Q* statistic (significant at  $P < .10$ ), and the extent of any observed heterogeneity was determined by  $I^2$  (ranging from 0% to 100%). The *Q* statistic failed to indicate statistical heterogeneity for the outcomes of death and nonfatal MI, whereas statistical heterogeneity was present for the end points of unplanned revascularization and angina. Since the absence of statistical heterogeneity does not guarantee clinical homogeneity, summary odds ratios (ORs) for all end points were calculated with the inverse variance method using a random-effects model from the ORs and 95% CIs for each end point in each study. The random-effects model provides a more conservative summary estimate because it incorporates both within-trial and between-trial variance.  $P < .05$  was considered statistically significant, and all tests were 2-sided unless otherwise indicated.

We further assessed potential associations of the treatment effect with study-level variables in subgroup analyses. A prespecified subgroup analysis was performed based on the requirement of ischemia for study entry vs no requirement for ischemia at study entry and for studies that enrolled patients prior to the year 2000 vs enrollment after 2000. Sensitivity analyses were performed for each outcome to determine whether any single study disproportionately influenced the pooled estimate by excluding individual trials one at a time and recalculating the combined OR for the remaining studies. To qualitatively assess publication bias, a funnel plot of the logarithm of effect size vs the standard error for each trial was gen-

erated. The Egger weighted linear regression test was used to examine the quantitative association between mean effect estimate and its variance.

## Results

### Literature Search

The electronic search yielded 2235 citations, which were screened by reviewing the title or abstract of each. Of these, 108 publications were reviewed in full, and 5 trials were included in the meta-analysis according to the PRISMA statement<sup>19</sup> for reporting systematic reviews and meta-analyses (Figure 1). These were the Medicine, Angioplasty, or Surgery Study II (MASS II),<sup>13</sup> the trial by Hambrecht et al,<sup>15</sup> Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE),<sup>17</sup> Bypass Angioplasty Revascularization 2 Diabetes (BARI 2D),<sup>14</sup> and the Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2 (FAME 2)<sup>16</sup> (Table 1). The 5 trials enrolled patients between 1997 and 2012 from Brazil, North America, and Europe. Funding was derived from government, university, and industry sources. The stress testing techniques used to diagnose ischemia are listed in Table 1. The stress tests were interpreted at the individual clinical sites. From the total enrollment of 5286 patients in these studies, 4064 were identified with myocardial ischemia at the time of randomization on the basis of stress testing or the presence of at least 1 hemodynamically significant coronary stenosis by FFR. Of these, 2016 patients were randomized to PCI and MT, and 2048 were randomized to MT alone. Baseline characteristics of the study populations are provided in Table 2. Patients enrolled in the studies were predominantly men. Patients with diabetes made up 22% to 100% of the study populations, and 25% to 40% of all patients had experienced a prior MI. Mean ejection fractions ranged from 57% to 69%. The extent of CAD ranged from single-vessel to 3-vessel dis-

Table 1. Characteristics of Included Trials

Source, Country or Region	Years of Enrollment	Inclusion Criteria	Exclusion Criteria	Techniques for Detection of Myocardial Ischemia	Criteria for Diagnosis of Ischemia	Total Participants/ With Ischemia, No.	Follow-up, y	Funding Source
MASS II, <sup>13</sup> Brazil	1997-2001	Angiographically documented proximal multivessel coronary stenosis of >70% by visual assessment and documented ischemia (stress testing or CCS class)	Refractory angina or acute MI, ventricular aneurysm, LVEF <40%, a history of PCI or CABG, single-vessel disease and normal or minimal CAD Left main disease ≥50%	Treadmill ECG testing	Clinical (angina) and/or ECG (magnitude of horizontal or down-sloping ST-segment depression) and/or scintigraphic (severity and extent of the perfusion defects)	408/165	5	University and national
Hambrecht et al, <sup>15</sup> Germany	1997-2001	Stable CAD and 1 native coronary artery stenosis of ≥75% by visual assessment by PCI CCS Class I-III with documented ischemia during stress ECG and/or SPECT imaging	Acute coronary syndrome (<2 mo), left main >25% or high-grade proximal LAD, LVEF <40%, prior PCI or CABG	Stress ECG and/or <sup>99m</sup> Tc scintigraphy	Presence of angina ST-segment changes ≥1 mm horizontal or down-sloping ST depression Presence of any perfusion defect	101/101	5	University and national
COURAGE, <sup>17</sup> North America	1999-2004	Stable CAD and CCS class IV angina (medically stabilized) At least 70% stenosis in at least 1 epicardial coronary artery and objective evidence of ischemia or at least 1 coronary stenosis of at least 80% and classic angina on provocative testing	Persistent CCS class IV angina Markedly positive stress test (substantial ST-segment depression or hypotensive response during stage 1 of Bruce protocol) Refractory heart failure or cardiogenic shock LVEF <30%, revascularization in the prior 6 mo, coronary anatomy not suitable for revascularization	Treadmill testing, exercise or pharmacologic stress imaging (nuclear or echocardiographic imaging)	Any of >1-mm ST deviation on standard treadmill exercise ECG; ≥1 scintigraphic perfusion defect during exercise technetium, <sup>99m</sup> Tc sestamibi, or thallium imaging; ≥1 perfusion defect (reversible or partial reversible) with pharmacologic (dipyridamole, adenosine) stress during <sup>99m</sup> Tc sestamibi or thallium imaging; ≥1 wall motion abnormality during exercise radionuclide ventriculography or 2-dimensional echocardiography (exercise or dobutamine)	2287/1938	4.6	Department of Veterans Affairs Cooperative Studies Program, Canadian Institutes of Health Research, supplemental support from industry
BARI 2D, <sup>14</sup> North and South America, Europe	2001-2005	Type 2 diabetes and CAD documented on angiography (≥50% stenosis of a major epicardial vessel associated with a positive stress test and classic angina)	Required immediate revascularization, left main disease, creatinine >2.0 mg/dL, Hgb A <sub>1c</sub> >13.0%, class III or IV heart failure, prior PCI or CABG	Treadmill testing, exercise or pharmacologic stress imaging (nuclear or echocardiographic imaging)	≥1-mm horizontal ST depression or down-sloping ST-segment depression or elevation for ≥60-80 milliseconds after the end of the QRS complex; myocardial perfusion defect; myocardial wall motion abnormality; decline in ejection fraction with stress; Doppler or pressure wire showing coronary flow reserve <2.0 or fractional flow reserve <0.75	1605/972	5	National Institutes of Health, additional support from industry
FAME 2 <sup>16</sup> Europe and North America	2010-2012	Stable CAD considered for PCI with at least 1 functionally significant stenosis (FFR≤0.80)	Patients in whom the preferred treatment is CABG Left main coronary artery disease Recent (<1 week) MI Prior CABG LVEF <30%	FFR	Pressure wire showing fractional flow reserve ≤0.80 during adenosine-induced hyperemia in at least 1 major coronary artery	888/888	0.59	Industry

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; ECG, electrocardiography; FFR, fractional flow reserve; Hgb, hemoglobin; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial

infarction; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography; <sup>99m</sup>Tc, technetium 99m.

SI conversion: To convert creatinine to micromoles per liter, multiply by 76.25.

ease. Stents were implanted in 66% to 100% of patients. Drug-eluting stents were used in 37% and 95% of patients in the BARI 2D<sup>14</sup> and FAME 2<sup>16</sup> studies, respectively. Medical therapy included aspirin, β-blockers, angiotensin-converting enzyme in-

hibitors, and statins (Table 2). All studies allowed crossover from MT to PCI for intolerable symptoms at the discretion of the treating physician. The median follow-up duration was 5 years.

Table 2. Characteristics of Patients With Documented Ischemia<sup>a</sup>

Characteristic	MASS II <sup>13</sup>		Hambrecht <sup>15</sup>		COURAGE <sup>17</sup>		BARI 2D <sup>14</sup>		FAME 2 <sup>16</sup>	
	MT+PCI	MT	MT+PCI	MT	MT+PCI	MT	MT+PCI	MT	MT+PCI	MT
Participants, No.	68	97	50	51	968	970	483	489	447	441
Age, mean, y	59	59	61	62	62	62	62	62	64	64
Male	62	79	100	100	86	85	73	73	80	77
Diabetes	22	31	22	24	33	35	100	100	28	27
Prior MI	38	33	40	51	35	40	26	25	37	37
Ejection fraction, mean	69	68	62	64	61	61	57	57	NR	NR
Vessels with stenosis >50%, mean No.	2.35	3.37	1.52	1.6	1.98	2.0	1.55	1.63	1.87	1.73
Stent placed	66	NA	100	NA	94	NA	90	NA	97	NA
Drug-eluting stent	0	NA	0	NA	3	NA	37	NA	95	NA
Medications										
Aspirin	100	97	98	98	93	93	97	95	87	90
β-Blocker	85	85	86	88	83	83	92	91	76	78
ACEI or ARB	28	28	88	75	74	73	94	94	69	70
Statin	74	59	80	71	89	90	96	96	83	82

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MI, myocardial infarction; MT, medical therapy; NA, not applicable; NR, not reported; PCI, percutaneous coronary intervention.

<sup>a</sup> Unless otherwise indicated, data are reported as percentage of participants.

Table 3. Quality Metrics of Included Studies

Source	Study Blinding	Blinding Technique	Random Assignment	Withdrawal Descriptions
MASS II <sup>13</sup>	No	No	Yes	Yes
Hambrecht et al <sup>15</sup>	No	No	Yes	Yes
COURAGE <sup>17</sup>	No	No	Yes	Yes
BARI-2D <sup>14</sup>	No	No	Yes	Yes
FAME 2 <sup>16</sup>	No	No	Yes	Yes

Table 4. Summary Odds Ratios for Major Outcomes of Percutaneous Coronary Intervention vs Medical Therapy

Outcome	Odds Ratio (95% CI)	P Value	Heterogeneity	
			Q (I <sup>2</sup> )	P Value
Death	0.90 (0.71-1.16)	.42	1.6 (0)	.80
Nonfatal MI	1.24 (0.99-1.56)	.06	0.52 (0)	.97
Unplanned revascularization	0.64 (0.35-1.17)	.14	39.2 (90)	<.001
Angina	0.91 (0.57-1.44)	.67	14.2 (72)	.007

Abbreviation: MI, myocardial infarction.

Study quality as assessed by the Jadad et al<sup>18</sup> criteria is summarized in Table 3. None of the trials was blinded. All of the studies were randomized and reported on study withdrawals and described the completeness of follow-up. All studies used an independent committee to adjudicate end points.

**Quantitative Outcomes**

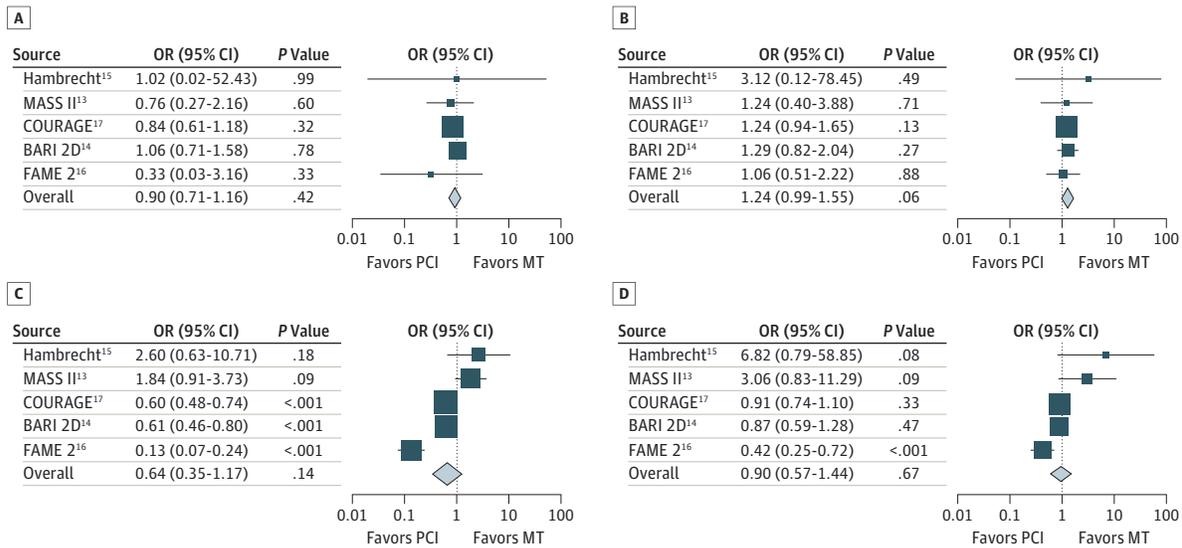
Table 4 summarizes the effect sizes for the main outcomes of the meta-analysis. Of the 281 deaths in the 4064 randomized patients with ischemia, 132 deaths occurred in the 2016 patients (6.5%) randomized to PCI, whereas 149 deaths occurred in the 2048 patients (7.3%) randomized to MT. The OR for PCI vs MT for mortality was 0.90 (95% CI, 0.71-1.16; P = .42; I<sup>2</sup> = 0%) (Figure 2A). Nonfatal MI was reported in 187 of 2016 patients (9.2%) in the PCI arms compared with 156 of 2048 patients (7.6%) in the MT arms of randomized trials. The OR for nonfatal MI for

PCI compared with initial MT was 1.24 (95% CI, 0.99-1.56; P = .06; I<sup>2</sup> = 0%) (Figure 2B). Unplanned revascularization was performed in 369 of 2016 PCI patients (18.3%) compared to 583 of 2048 medical therapy patients (28.4%). The OR for unplanned revascularization in the PCI vs MT patients was 0.64 (95% CI, 0.35-1.17; P = .14; I<sup>2</sup> = 90%) (Figure 2C). Among the patients randomized to PCI, 410 of 2016 (20.3%) had recurrent or persistent angina compared with 478 of 2048 (23.3%) randomized to MT (OR, 0.91; 95% CI, 0.57-1.44; P = .67; I<sup>2</sup> = 72%) (Figure 2D).

**Subgroup Analyses**

Subgroup analysis showed that the requirement for ischemia at study entry<sup>15,16</sup> did not make a significant difference for any of the 4 end points considered. Trials that enrolled patients prior to 2000<sup>13,15,17</sup> had OR for each end point similar to those of trials that enrolled all patients after 2000.<sup>14,16</sup>

**Figure 2.** Comparison of Percutaneous Coronary Intervention (PCI) and Medical Therapy (MT) vs Medical Therapy Alone in Patients With Documented Myocardial Ischemia



Each graph illustrates an outcome. A, Death; B, nonfatal myocardial infarction; C, unplanned revascularization; and D, angina during follow-up. All included studies are listed by name along with point estimates of the odds ratios (ORs)

and respective 95% CIs. The sizes of the squares denoting the point estimate in each study are proportional to the weight of the study. The diamonds represent the overall findings in each plot.

### Sensitivity Analyses and Publication Bias

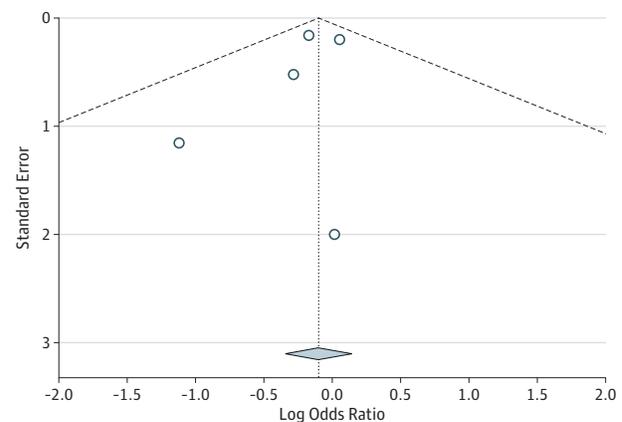
Sensitivity analyses to assess the potential impact of qualitative differences in study design and patient selection showed that exclusion of any single trial from the analysis for mortality, nonfatal MI, and angina did not alter the overall findings of the analysis (data not shown). However, removal of MASS II<sup>13</sup> data from the unplanned revascularization meta-analysis resulted in a statistically significant reduction in the OR for revascularization in favor of the PCI group compared with the MT group (OR, 0.49 [95% CI, 0.26-0.91] (*P* = .02). The exclusion of data from FAME 2,<sup>16</sup> which was the only study to exclusively use FFR rather than conventional stress testing, the only study funded entirely by industry, the study with the shortest follow-up, and the only study that predominantly used drug-eluting stents, did not change the overall results for any end point.

The funnel plot was symmetric, suggestive of a lack of publication bias (Figure 3). The Egger test further supported the absence of publication bias with a 1-tailed *P* value of .22.

### Discussion

The principal finding of this meta-analysis of randomized clinical trials of patients with stable obstructive CAD and myocardial ischemia documented by stress testing or FFR is that a strategy of initial PCI in combination with MT results in no significant reduction in mortality, nonfatal MI, unplanned revascularization, or angina compared with MT alone. These findings are unique in that this is the first meta-analysis to our knowledge limited to patients with documented, objective findings of myocardial ischemia, almost all of whom under-

**Figure 3.** Assessment of Publication Bias



This funnel plot is a plot of a measure of study size on the vertical axis as a function of effect size on the horizontal axis for mortality. Large studies appear toward the top of the graph and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. In the absence of publication bias, as demonstrated in this funnel plot, the studies, represented by pale dotted circles, are distributed symmetrically about the combined effect size. The dashed diamond appearing below the x-axis represents the summary effect.

went treatment with intracoronary stents and disease-modifying secondary prevention therapy. The implications of these findings are 3-fold. First, the results strongly suggest that the relationship between ischemia and mortality is not altered or ameliorated by catheter-based revascularization of obstructive, flow-limiting coronary stenoses. Second, the lack of

clinical benefit from PCI in patients with inducible ischemia suggests that the genesis of late clinical events is not necessarily a consequence of the ischemic vascular territory subtending a stenotic coronary segment but rather due to the development of new plaque ruptures in distant coronary segments without flow-limiting stenoses. Finally, these findings call into question the common practice of ischemia-guided revascularization (either using noninvasive testing techniques or FFR) where the presence of myocardial ischemia routinely determines patient selection for coronary angiography and revascularization.

The seminal studies of Brown et al<sup>20</sup> and Ladenheim et al<sup>21</sup> introduced the concept of stress testing for the assessment of prognosis in patients with CAD. Since that time, several hundred papers have reported on the prognostic value of exercise treadmill testing,<sup>22</sup> stress echocardiography,<sup>5-7</sup> myocardial perfusion imaging,<sup>23-26</sup> and most recently, stress myocardial perfusion with positron emission tomography.<sup>27</sup> These studies have consistently demonstrated that patients with more extensive and severe ischemia experience increased long-term mortality or reduced event-free survival compared with patients without ischemia. The assumption that this ischemia-mortality association is mediated by an obstructive coronary stenosis has been used to justify coronary angiography and revascularization<sup>26,28-30</sup> in patients with ischemia.

However, while this ischemia-driven approach to PCI is a cornerstone of daily practice in the evaluation of patients with chest pain or known CAD—endorsed by the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines<sup>28-30</sup> and reiterated in recent reviews<sup>8,31,32</sup>—there are scant data supporting it. A single retrospective observational study of over 10 000 patients who underwent exercise or adenosine myocardial perfusion scintigraphy from 1991 to 1997 found that revascularization in patients with moderate to large amounts of myocardial ischemia was associated with a reduction in the risk of cardiac death on Cox analysis compared with MT alone.<sup>4</sup> While the specific components of MT were not described in this propensity-matched analysis, MT in the 1990s did not reflect contemporary concepts of guideline-directed MT that includes disease-modifying therapies such as statins, inhibitors of the renin angiotensin system,  $\beta$ -blockers, and thienopyridines.<sup>33</sup> Furthermore, observational studies are intrinsically biased by unidentifiable confounders that are not completely adjusted for by propensity methods.<sup>34</sup>

In contrast, 2 more recent substudies of the COURAGE trial failed to demonstrate that PCI conferred a reduction in mortality or MI compared with MT in patients with myocardial ischemia.<sup>11,12</sup> The first study<sup>11</sup> analyzed a subset of 314 of the 2287 COURAGE patients (13.7%) who had non-protocol-mandated serial gated stress perfusion imaging with sestamibi before and 6 to 18 months after randomization. Percutaneous coronary intervention was found to be more effective than MT at reducing moderate to severe ischemia, but while it appeared to reduce death and MI on unadjusted analysis, that benefit did not persist after risk adjustment. Despite the lack of clinical benefit associated with PCI in this small substudy, these results have been repeatedly used to justify a strategy of ischemia-based revascularization.<sup>8,32,35</sup>

The second and more recent study<sup>12</sup> enrolled 1381 of the 2287 COURAGE patients (60%) who had a baseline stress myocardial perfusion single-photon emission computed tomographic imaging study. Patients were divided into 2 groups—those with no or mild ischemia and those with moderate to severe ischemia. Percutaneous coronary intervention was not associated with a reduction in death or MI compared with MT alone in either group, findings that were discordant from the earlier COURAGE substudy.<sup>11</sup>

Although it remains unclear how myocardial ischemia confers increased mortality risk, our results in combination with those of prior research suggest that myocardial ischemia may be more of a marker for atherosclerotic burden, with the increased propensity of future events being mediated by the volume of atherosclerotic plaques at risk of becoming unstable, rupturing, and inciting thrombosis and MI rather than by progressive fibroatherosclerotic coronary disease. In support of this concept, patients with myocardial ischemia have a greater atherosclerotic plaque burden as measured by calcium score than those without ischemia.<sup>36</sup> This concept is also consistent with the 25-year-old observation that the vast majority of plaques responsible for acute MI emanate from stenoses of less than 70% by angiography prior to the acute event.<sup>37</sup> Thus, the lesions that are responsible for most cases of MI and subsequent death are not severe enough to induce ischemia on stress testing, and the lesions responsible for causing ischemia do not tend to rupture. Since intervening on a marker of an outcome that is not in the causal pathway of the subsequent adverse clinical events would not be expected to reduce those events, it should not be surprising that prior clinical trials<sup>14,17</sup> and meta-analyses<sup>33,38-40</sup> consistently demonstrate that PCI fails to reduce death or MI in patients with stable CAD who are concomitantly aggressively treated with contemporary medical therapy for secondary prevention.

The persistence of angina in over 20% of patients in both arms of the present study suggests that, similar to death and MI, this important symptom is not exclusively mediated by flow-limiting stenoses. Rather, other pathogenetic mechanisms appear to be involved, including inflammation, endothelial dysfunction, microvascular disease, coronary vasospasm, thrombosis, and angiogenesis.<sup>41</sup> In most patients, because MT is systemic treatment, it is better able to address these components than PCI, which is targeted only focally to treat a specific stenotic coronary segment.

As pointed out by Califf,<sup>42</sup> although the ischemia-guided approach to revascularization is conceptually appealing, it has notable inconsistencies, including the inability to make an asymptomatic patient feel better, the inability of PCI to prevent MI, and the inevitable complications of PCI, including death, stroke, MI, and hemorrhage at the access site. The present study confirms and extends these inconsistencies by demonstrating that not only does PCI not reduce the likelihood of MI, it also offers no durable benefit in terms of reduced mortality, need for revascularization, or occurrence of angina in patients with stable obstructive CAD and myocardial ischemia. Furthermore, since ischemia does not identify patients who clinically benefit from revascularization, this study calls into question the use of nuclear stress testing or measure-

ment of FFR in patients with documented CAD but without limiting symptoms, as is currently considered appropriate and widely practiced.<sup>43</sup>

Our analysis should be interpreted within the context of several limitations. First, complete information on the extent and severity of myocardial ischemia was not available for all studies, limiting this analysis to patients with any degree of objectively documented ischemia. Although recent data suggest no benefit of PCI in reducing death or MI in patients with both mild and moderate to severe ischemia,<sup>12</sup> this issue will be definitively addressed by the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) Trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) Identifier NCT01471522), funded by the National Heart, Lung, and Blood Institute. This study of 8000 patients with at least moderate myocardial ischemia will compare the effect of MT combined with revascularization with that of MT alone on cardiovascular death and MI.

Second, in COURAGE<sup>17</sup> and BARI 2D,<sup>14</sup> patients were not mandated to undergo stress testing. Thus, it is possible that patients who underwent stress testing in those studies are not representative of the entire study population. However, this is unlikely in light of a recent meta-analysis<sup>33</sup> that included the entire COURAGE and BARI 2D cohorts and found results identical to those of the present study.

Third, only the FAME 2 study<sup>16</sup> used a predominance of drug-eluting stents. It is likely that some of the unplanned revascularizations in the PCI arms of the other studies were necessitated by restenosis of a bare metal stent, which might have been avoided had a drug-eluting stent been placed originally. Fourth, the trials included in this meta-analysis enrolled only those patients with CAD considered appropriate for revascularization with PCI. Thus, these results do not apply to patients with CAD for whom CABG would be the preferred mode of revascularization. Finally, data were extracted from only randomized controlled trials and, therefore, may not be representative of patients seen in daily practice.

## Conclusions

For patients with stable obstructive CAD and objective evidence of myocardial ischemia, a strategy of initial PCI and MT does not confer benefit in terms of reduction of death, MI, repeat revascularization, or angina compared with MT alone. These findings underscore existing clinical practice guidelines that recommend an initial approach of contemporary MT for patients with stable CAD and ischemia rather than proceeding directly to ischemia-guided PCI.<sup>30</sup>

### ARTICLE INFORMATION

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