

Meta-Analysis of Trials on Mortality After Percutaneous Coronary Intervention Compared With Medical Therapy in Patients With Stable Coronary Heart Disease and Objective Evidence of Myocardial Ischemia



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Outcomes of percutaneous coronary intervention (PCI) versus medical therapy (MT) in the management of stable ischemic heart disease (SIHD) remain controversial, with some but not all studies showing improved results in patients with ischemia. We sought to elucidate whether PCI improves mortality compared to MT in patients with objective evidence of ischemia (assessed using noninvasive imaging or its invasive equivalent). We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing PCI to MT in patients with SIHD. To maintain a high degree of specificity for ischemia, studies were only included if ischemia was defined on the basis of noninvasive stress imaging or abnormal fractional flow reserve. The primary outcome was all-cause mortality. We identified 3 RCTs (Effects of Percutaneous Coronary Interventions in Silent Ischemia After Myocardial Infarction II, Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2, and a substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial) enrolling a total of 1,557 patients followed for an average of 3.0 years. When compared with MT in this population of patients with objective ischemia, PCI was associated with lower mortality (hazard ratio 0.52, 95% confidence interval 0.30 to 0.92, $p = 0.02$). There was no evidence of study heterogeneity or bias among included trials. In this meta-analysis of published RCTs, PCI was shown to have a mortality benefit over MT in patients with SIHD and objective assessment of ischemia using noninvasive imaging or its invasive equivalent. In conclusion, this study provides insight into the management of a higher-risk SIHD population that is the focus of the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:1194–1199)

Randomized controlled trials (RCTs), including the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and the Revascularization Investigation 2 Diabetes trials, have called into question whether percutaneous coronary intervention (PCI) reduces death or myocardial infarction (MI) in patients with stable ischemic heart disease (SIHD) relative to medical therapy

(MT) alone.^{1,2} However, these trials randomized a broad population both with and without objective evidence of ischemia. In this regard, most previous studies have reported that objective evidence of myocardial ischemia bears both a qualitative and quantitative relation with subsequent clinical outcomes including death and nonfatal MI.^{3–7} To address this issue, the ongoing National Heart, Lung and Blood Institute–funded International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (Identifier NCT01471522) is being conducted to evaluate ischemia-based revascularization for patients with moderate or severe ischemia. Pending these results, we performed a meta-analysis of existing RCTs comparing PCI with MT in patients with documented myocardial ischemia to elucidate whether objective ischemia may determine who may benefit from PCI versus MT alone.

Methods

The present study prespecified 2 important inclusion criteria: Given the low diagnostic accuracy of exercise treadmill testing (ETT) with solely symptom-based or

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See page 1197 for disclosure information.

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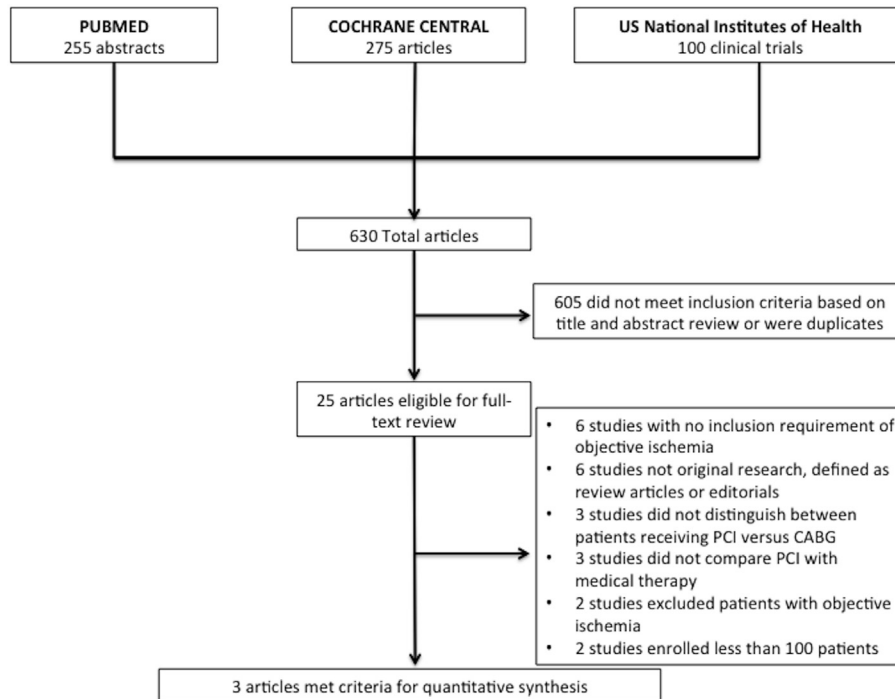


Figure 1. Flowchart of selected studies.

Table 1
Characteristics of included studies

Trial	Ischemia Testing; Primary Endpoint	Median Time to Follow-up
COURAGE Nuclear Substudy 0 ¹¹	Moderate-to-severe defined as ≥ 3 ischemic segments on nuclear imaging; Composite of death from any cause or MI	4.6 years
FAME 2 ¹²	Fractional flow reserve of ≤ 0.80 ; Composite of death from any cause, nonfatal MI, or urgent revascularization	7 months
SWISSI II ¹³	Symptom-limited ETT with ST depression and confirming stress imaging; Cardiac death, nonfatal MI, and/or revascularization	10.2 years

COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; ETT = exercise treadmill testing; FAME 2 = Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; MI = myocardial infarction; SWISSI = Silent Ischemia After Myocardial Infarction.

electrocardiographic assessment of ischemia, we required ischemia to be documented by either noninvasive stress imaging or abnormal fractional flow reserve (FFR).⁸ Moreover, previous studies have most often focused on a primary end point of death or MI. As the definition of MI in these studies varies considerably between trials and as periprocedural and spontaneous MIs may have very different prognostic implications, all-cause mortality was chosen as the principal end point for the present analysis, which should reduce definitional and ascertainment bias of MI.⁹

We searched for RCTs published from January 1980 to May 2013 that compared MT with PCI to MT alone in patients with

Table 2
Baseline patient characteristics

Variable	COURAGE Nuclear Substudy 0 ¹¹		FAME 2 ¹²		SWISSI II ¹³	
	PCI + MT	MT	PCI + MT	MT	PCI + MT	MT
Participants (n)	223	245	447	441	96	105
Age (mean, years)	62	62	64	64	54	56
Women	14%	13%	20%	23%	12%	13%
Cardiac risk factors						
Hyperlipidemia	44%	49%	74%	79%	75%	58%
Hypertension	69%	71%	78%	78%	45%	45%
Diabetes	32%	39%	28%	27%	9%	13%
Current smoker	29%	24%	20%	20%	73%	74%
Prior MI	40%	39%	37%	38%	NR	NR
Prior PCI	13%	14%	18%	17%	NR	NR
CCS class						
0	15%	13%	12%	11%	NR	NR
I	28%	34%	18%	22%	NR	NR
II	35%	36%	46%	45%	NR	NR
III	22%	17%	18%	15%	NR	NR
Medications						
Antiplatelet	93%	91%	87%	90%	NR	NR
Anti-lipid	75%	69%	83%	82%	NR	NR
Beta-blocker	72%	68%	76%	78%	NR	NR
ACE-inhibitor or ARB	54%	57%	69%	70%	NR	NR

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCS = Canadian Cardiovascular Society; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME 2 = Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; MI = myocardial infarction; MT = medical therapy; PCI = percutaneous coronary intervention; SWISSI = Silent Ischemia After Myocardial Infarction.

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