Interpreting the Results of the COURAGE Trial: A Non-Interventionalist Perspective

William E. Boden, MD, FACC, FAHA

Department of Medicine and Preventive Medicine, University at Buffalo Schools of Medicine and Public Health, Buffalo, NY; Cardiovascular Services, Kaleida Health, Buffalo, NY; Buffalo General and Millard Fillmore Hospitals, Buffalo, NY

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial was designed to determine whether percutaneous coronary intervention (PCI) coupled with optimal medical therapy (OMT) reduced the risk of death or nonfatal myocardial infarction in patients with stable coronary artery disease as compared with OMT alone. COURAGE demonstrated that an initial strategy of PCI added to OMT in these patients relieved angina to a greater extent than an initial strategy of OMT alone for a period of approximately 24 months. The initial strategy of PCI (plus OMT) did not reduce death, myocardial infarction, or other major cardiovascular events compared with OMT alone. The important quality-of-life findings permit physicians to engage in an evidence-based discussion with patients about the expected clinical and health status benefits of initial versus deferred PCI when added to OMT.

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Since the advent of percutaneous coronary intervention (PCI) in 1977, the ability to mechanically dilate obstructive coronary artery stenoses has fundamentally altered our approach to managing patients with coronary artery disease (CAD). Over the decades, the remarkable and sustained evolution of this catheter-based technology has shifted treatment largely away from an initial pharmacologic approach to one that emphasized an anatomically-driven management strategy. Importantly, over this same time period, significant advances occurred in our understanding of the pathophysiologic basis for acute

coronary syndromes and the important role that plaque rupture or fissure plays in the genesis of acute myocardial infarction (MI), which clearly indicate that non–flow-limiting coronary stenoses are the principal progenitors of most "hard" clinical events.[1-3] We now recognize that total or subtotal coronary occlusion following plaque rupture or fissuring is a cardiovascular emergency that cannot be optimally managed pharmacologically. Abundant trial data support the belief that urgent/emergent PCI in patients with ST-segment elevation myocardial infarction (STEMI) or high-risk non-STEMI confers a prognostically important reduction in death or subsequent MI.[4-9]

Because elective PCI in patients with chronic stable angina is virtually identical procedurally to that performed in acute coronary syndrome (ACS) patients, many have accepted the broader (but unproven) premise that PCI would confer a more durable clinical benefit (ie, beyond mere angina relief or improved exercise performance) in this population of patients as well. Accordingly, the management of stable angina has been based largely on the "conventional wisdom" that the triad of angina, objective evidence of myocardial ischemia, and the presence of 1 or more flow-limiting coronary stenoses necessitated revascularization as the sine qua non of optimal treatment.

Principal Findings of the COURAGE Trial

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial was designed to determine whether PCI coupled with optimal medical therapy (OMT) reduces the risk of death or nonfatal MI in patients with stable CAD, as compared with OMT alone.[10,11] Such a robust "strategy trial" had never been conducted since the advent of angioplasty in 1977, although there were 11 prior studies that compared PCI *in apposition to*—not *in combination with*—OMT.[12] COURAGE enrolled 2287 patients with objective evidence of myocardial ischemia and significant CAD from 50 US and Canadian centers. Between 1999 and 2004, 1149 patients were assigned to PCI with OMT, and 1138 were assigned to OMT alone. The primary outcome was all-cause mortality or nonfatal MI during a 2.5- to 7.0-year (median, 4.6-year) follow-up. Major clinical outcomes are summarized in Table 1 and Figure 1. There were 211 primary events in the PCI group and 202 events in the medical therapy group. The 4.6-year cumulative primary event rates were 19.0% and 18.5% in the PCI and medical therapy groups, respectively (hazard ratio [HR] in the PCI group compared with the medical therapy group, 1.05; 95% confidence interval [CI], 0.87-1.27; $P = .62$). Comparing PCI and medical therapy groups, there were no differences in death, MI, or stroke (20.0% vs 19.5%; HR, 1.05; 95% CI, 0.87-1.27; $P = .62$); hospitalization for ACS (12.4% vs 11.8%; HR, 1.07; 95% CI, 0.84-1.37; $P = .56$); or MI (13.2% vs 12.3%; HR, 1.13; 95% CI, 0.89-1.43; $P = .33$).[11] Thus, the main study findings indicate that, *as an initial management strategy in patients with stable CAD*, PCI did not reduce death, MI, or other major cardiovascular events when added to OMT.

Importantly, the Kaplan-Meier lifetable curves for the primary outcome measure of death or MI were virtually superimposable for the 2 randomized groups over the initial 4.5 years of follow-up (HR, 1.05; 95% CI, 0.87-1.27). In fact, the 95% CI excludes a potential benefit of PCI of greater than 13%, which means that there is only a 5% chance that a death or MI reduction with PCI is 13% or greater (ie, only a 5% probability that the absolute risk reduction of PCI is no greater than 2.47% [4.6 year median death/MI rate for PCI = 0.19 × 0.13 = 0.0247]).[11] Thus, it is exceedingly unlikely that a true PCI benefit was missed.

Additionally, cause-specific cardiac outcomes from the COURAGE trial have also recently been published.[13] Major cardiovascular outcomes are summarized in Table 2. The composite of cardiac death or MI occurred in 172 patients (15%) in the PCI group and in 162 patients (14.2%) in the OMT group (HR, 1.07; 95% CI, 0.86-1.33; $P = .62$). This HR was identical to the trial primary outcome measure of all-cause mortality or MI that was published previously.[11] The composite of cardiac death, MI, or ACS occurred in 270 patients (23.5%) in the PCI group and in 257 patients (22.6%) in the OMT group (HR, 1.07; 95% CI, 0.91-1.27; $P = .60$) (Figure 2). The time to first event for the composite of cardiac death, MI, ACS, or stroke was observed in 313 patients (27.2%) in the PCI group as compared with 305 patients (26.8%) in the OMT group (HR, 1.05; 95% CI, 0.89-1.22; $P = .51$). Overall, all composite cardiovascular outcomes showed no significant between-group differences[13] and paralleled closely the primary and secondary composite outcomes of the trial as a whole, including all-cause mortality.

Thus, the main study findings[11] and recent cause-specific outcomes[13] indicated that, *as an initial management strategy in patients with stable CAD*, PCI did not reduce death, MI, or other major cardiovascular events when added to OMT. Clearly, when these findings were first presented and published in 2007, there was an intense controversy and criticism of the main study findings, although it

Table 1
Baseline Clinical and Angiographic Characteristics*

Characteristic	PCI + Optimal Medical Therapy (N = 1149)	Optimal Medical Therapy (N = 1138)	*P* Value
Clinical and Demographic			
Age (years)	61.5 ± 10.1	61.8 ± 9.7	.54
Sex, no. (%)			
Male	979 (85)	968 (85)	.95
Female	169 (15)	169 (15)	
Race or Ethnic Group, no. (%)			
White	988 (86)	975 (86)	.64
Black	57 (5)	57 (5)	
Hispanic	68 (6)	58 (5)	
Other	35 (3)	47 (4)	
Angina			
CCS Class, no. (%)			
Missing	3 (0)	2 (0)	
0	135 (12)	148(13)	.24
1	340 (30)	341(30)	
2	409 (36)	425(37)	
3	261 (23)	221 (19)	
Median Duration of Angina (months)†	5 (1,15)	5 (1,15)	.53
Median Episodes per Week With Exertion or at Rest, Last Month†	3 (1, 6)	3 (1, 6)	.83
History, no. (%)			
Diabetes	367 (32)	399 (35)	.12
Hypertension	757 (66)	764 (67)	.53
Congestive Heart Failure	57 (5)	51 (5)	.59
Cerebrovascular Disease	100 (9)	102 (9)	.83
Myocardial Infarction	437 (38)	439 (39)	.80
Prior PCI	174 (15)	185 (16)	.49
CABG	124 (11)	124 (11)	.94
Stress Test, no. (%)‡			
Total Patients With Any Stress Test	1093 (95)	1075 (94)	
Treadmill Test	555 (48)	553 (49)	.84
Pharmacologic Stress	417 (43)	424 (43)	
Echocardiographic	63 (6.6)	54 (5.6)	
Duration of Treadmill Test (minutes)	7.0 ± 2.7	6.9 ± 2.3	.43
Nuclear Imaging	685 (60)	708 (62)	.59
Single Reversible Defect§	154 (22)	161 (23)	.08
Multiple Reversible Defect§	444 (65)	483 (68)	
Angiographic			
No. Vessels Diseased (%)			
1	361 (31)	343 (30)	
2	446 (39)	439 (39)	.72
3	341 (30)	355 (31)	

Table 1
(Continued)

Characteristic	PCI + Optimal Medical Therapy (N = 1149)	Optimal Medical Therapy (N = 1138)	*P* Value
Disease in Graft[¶]	77 (63)	85 (69)	.36
Proximal LAD Disease	360 (31)	417 (37)	.01
Ejection Fraction	60.8 ± 11.2	60.9 ± 10.3	.86

*One patient in each treatment group had missing baseline data. Plus-minus values are means ± standard deviation.
[†]Median and interquartile range.
[‡]Nuclear imaging could be done after either exercise treadmill testing stress or pharmacologic stress.
[§]Percent of those with imaging.
[¶]Percent of those having CABG.
CABG, coronary artery bypass graft surgery; CCS, Canadian Cardiovascular Society; MI, myocardial infarction.
Adapted with permission from Boden WE et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007;356:1503-1516.[11]

Figure 1. *Major clinical outcomes in the COURAGE trial. ACS, acute coronary syndrome; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention. Adapted with permission from Boden WE et al. Optimal medical therapy with or without PCI for stable coronary disease.* N Engl J Med. *2007;356:1503-1516.[11] Copyright © 2007 Massachusetts Medical Society. All rights reserved.*

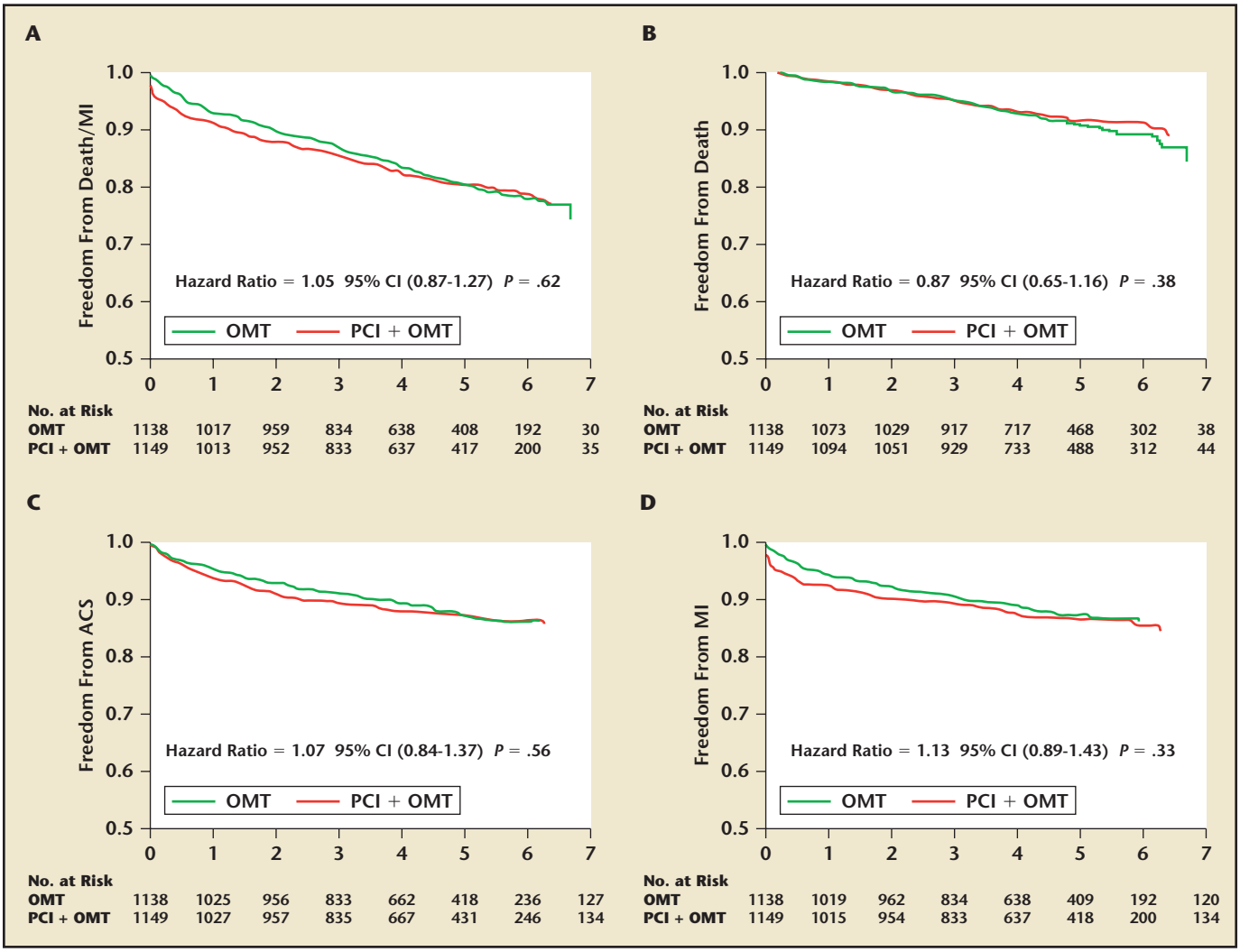

Table 2
Cardiovascular Outcomes

Outcome	PCI + OMT (N = 1149)	OMT (N = 1138)	HR (95% CI)	*P* Value
Cardiac Death	39 (3.4%)	44 (3.9%)	0.87 (0.56-1.33)	.51
Cardiac Death/MI	172 (15%)	162 (14.2%)	1.07 (0.86-1.33)	.62
Cardiac Death/MI/ACS	270 (23.5%)	257 (22.6%)	1.07 (0.91-1.27)	.60
Cardiac Death/MI/Stroke	188 (16.4%)	173 (15.2%)	1.10 (0.89-1.35)	.45
Cardiac Death/MI/ACS/Stroke	313 (27.2%)	305 (26.8%)	1.05 (0.89-1.22)	.51
MI/Stroke	160 (13.9%)	139 (12.2%)	1.16 (0.93-1.46)	.23
Total MI	147 (12.8%)	126 (11.1%)	1.14 (0.90-1.44)	.48
Total MI, Spontaneous	109 (10.4%)	113 (9.5%)	0.91 (0.70-1.18)	.46
Total Peri-PCI MI	37 (3.4%)	11 (1.0%)	3.57 (1.83-6.96)	< .001
Total Peri-CABG MI	1	2		
Total ACS	136 (11.8%)	125 (11.0%)	1.08 (0.85-1.38)	.52
Total Stroke	22 (1.9%)	14 (1.2%)	1.56 (0.80-3.05)	.19

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.
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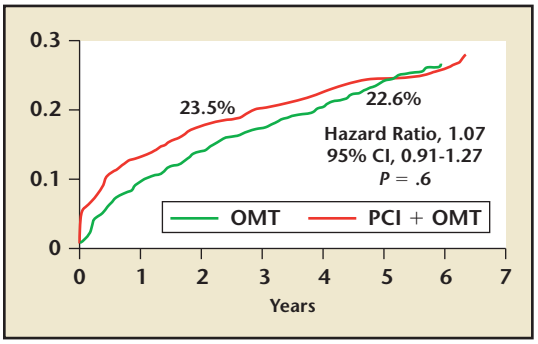


Figure 2. *Tertiary outcomes—cardiac death/myocardial infarction/acute coronary syndrome—in the COURAGE trial. ACS, acute coronary syndrome; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention. Reprinted from* American Journal of Cardiology. *Volume 104, Number 1. Boden WE et al. Impact of optimal medical therapy with or without percutaneous coronary intervention on long-term cardiovascular end points in patients with stable coronary artery disease (from the COURAGE trial). Pages 1-4.[13] Copyright © 2009, with permission from the American College of Cardiology.*

now appears that there has been greater acceptance of the trial results and their therapeutic implications.

The Non-Interventionalist Perspective of COURAGE

"COURAGE Tells Us Nothing New . . ."

Perhaps as a response to minimize the significance of the trial findings, a common, initial interpretation of the COURAGE trial was that the results were not unexpected and hence were merely confirmatory of what had been largely accepted by the cardiology and broader general physician community. Many influential academic and practicing cardiologists were seemingly dismissive of the principal study finding that there was no incremental benefit of PCI on top of a background of OMT in the majority of patients with stable ischemic heart disease (SIHD).[14] Yet, this trial has added significantly to the relative void of published scientific information about the prognostic role of PCI in reducing long-term "hard" clinical events (ie, death or MI) in a common population of SIHD patients with ischemia and significant angiographic CAD, such as occurs in millions of patients worldwide. Prior to COURAGE, the randomized, controlled trials (RCTs) that have addressed prospectively the potential benefit of PCI versus medical therapy comprised fewer than 3000 patients in 11 trials,[12] which is hardly the basis for a conclusion that the neutral results merely confirmed existing scientific knowledge. Excluding the Second Randomized Intervention Treatment of Angina (RITA-II) trial[15] of 1018 patients, the remaining 10 RCTs involved fewer than 1950 patients.[12] Thus, given the paucity of prospectively-derived data in such limited numbers of largely low-risk patients, it is simply unsound scientifically to assert that "COURAGE merely tells us what we already know," particularly considering that tens of millions of patients worldwide with stable CAD have undergone PCI electively for chronic angina over the past 30 years.

Importantly, the medical therapy as used in COURAGE was far more extensive and comprehensive than

ever undertaken previously in any long-term clinical outcomes trial of SIHD patients. In the earlier studies comparing PCI with medical therapy that date back to the mid-1980s, medical therapy consisted principally of aspirin, long-acting nitrates, and β-blockers. These historically-dated studies antedated the use of statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, and more powerful, adjunctive antiplatelet/anticoagulant therapy, as is used in contemporary practice.

Intensity of OMT and Importance of Achieving Treatment Targets

Most cardiovascular clinical trials test a single intervention. COURAGE tested a comprehensive set of lifestyle and pharmacologic interventions as part of OMT with or without PCI in patients with SIHD. Unlike earlier studies that used only modest anti-ischemic therapy as the comparator, COURAGE sought to use aggressive medical therapy of each important drug class (eg, aspirin, β-blockers, ACE inhibitors, statins) that had been proven to be of clinical benefit in individual, placebo-controlled RCTs. In COURAGE, these pharmacologic agents were used in the aggregate and applied equally to both the PCI and OMT groups so as not to deprive the PCI arm of the putative benefits associated with intensive secondary prevention. No other trial had ever attempted such a comprehensive treatment approach in SIHD patients, nor had any preceding trial ever attempted to incorporate guideline-driven best practices to achieve and maintain multiple treatment targets during long-term follow-up.

All patients, regardless of treatment assignment, received equivalent lifestyle and pharmacologic interventions for secondary prevention and angina therapy. Most medications were provided at no cost. Therapy was administered by nurse case managers according to protocols to achieve predefined lifestyle and risk factor goals. Of the 2287 patients who were followed for a median 4.6 years, there were no significant differences between treatment groups in the percentage of patients achieving therapeutic goals.[11] At baseline, 23% of subjects smoked, which fell to 19% during the trial. Food choices and level of physical activity improved, but body mass index remained unchanged at approximately 29 kg/m^2. Medication use changed from baseline to 60 months as follows: antiplatelet agents: 97% to 96%; β-blockers: 85% to 88%; renin-angiotensin system inhibitors: 61% to 72%; and statins: 89% to 93%. Systolic blood pressure fell from 130 mm Hg to 123 mm Hg. Low-density lipoprotein cholesterol fell from 101 mg/dL at baseline to 71 mg/dL at 60 months of follow-up. Thus, aggressive secondary prevention and guideline-driven therapy[11] were applied equally and intensively to both treatment groups in COURAGE by nurse case managers using treatment protocols. As such, OMT as used in COURAGE represents a model for secondary prevention in clinical practice.

A notable strength of the COURAGE trial was the hypothesis that a combination of PCI directed at focal flow-limiting stenoses causing chronic angina and ischemia, combined with disease-modifying therapies such as statins, renin-angiotensin system inhibitors, and β-blockers as a fundamental part of OMT, would be inherently superior to OMT alone in reducing prognostically-important clinical endpoints during long-term follow-up. Intuitively, the combination of both a *focal* and *systemic* approach to CAD management would be plausibly expected to mitigate cardiac events better than a systemic approach alone in SIHD patients with extensive angiographic CAD, significant inducible ischemia, and appreciable clinical comorbidity. The clinical, noninvasive stress test findings and coronary angiographic features of the study group are summarized in Table 2, and highlight the fact that this was not a low-risk population. On the contrary, the median 4.6-year composite rate of death or MI was 19%, and the composite rate for cardiovascular death, MI, stroke, and hospitalization for ACS was 27%. These findings are consistent with at least an "intermediate-risk" profile.[10,11]

It has been argued by some critics that the "optimal medical therapy" as used in COURAGE was "too good" and cannot be replicated in routine clinical practice.[14] Contrary to the perception that the COURAGE investigators and study coordinators went to extraordinary lengths to ensure that patients complied with OMT or were seen at multiple time intervals to reinforce protocol adherence, after the first year of follow-up (when patients were seen at 3-month intervals), follow-up visits between years 1 and 7 were scheduled only at 6-month intervals. Investigators and coordinators worked closely with referring physicians to underscore the importance of maintaining medical therapy and lifestyle changes and treating patients to multiple treatment targets. Indeed, in most busy clinical cardiology practices today (either office-based or hospital-based), the use of physician extenders such as nurse practitioners and/or physician assistants can provide an important, additional source of manpower to replicate the approach that was used in COURAGE to achieve treatment adherence and therapeutic targets for blood pressure, lipids, and glycemic control.

In a recent thoughtful review,[16] several interventional cardiology opinion leaders said the following about the importance of OMT as used in COURAGE: "In these trials of patients with stable CAD . . . no reduction in death and MI has been observed, and these limitations of PCI in this clinical setting need to be emphasized. . . . OMT forms the cornerstone of management for any patient with CAD. . . ."

Would Greater DES Usage or More "Complete" Revascularization Have Changed the COURAGE Results?

The use of drug-eluting stents (DES) was low (< 3%) in COURAGE, in part because these devices were not approved by the Food and Drug administration until the last 6 months of patient accrual. Although the use of DES might have further improved angina-free outcomes in the PCI arm, and likely would have resulted in a lower incidence of repeat revascularization than the 21% reported for the PCI group during a median 4.6-year follow-up, there are no data whatsoever to support the superiority of DES as compared with bare-metal stents in reducing death or MI based on several randomized trials and recent meta-analyses.[17-20] Thus, it is highly unlikely that greater use of DES would have measurably altered the primary outcome in COURAGE.

Among the 94% of COURAGE trial patients who underwent coronary stenting, 59% of patients received 1 stent and 41% of patients received 2 or more stents.[11] Because 69% of patients in COURAGE had significant multivessel CAD at angiography, the discordance between this percentage and the 41% multiple stent usage rate has been interpreted by some as a manifestation of "incomplete revascularization" which, in turn, is cited as a potential explanation for the lack of benefit for PCI on clinical outcomes. However, it has not yet been proven whether clinical outcomes (death or MI) can be improved with more "complete" revascularization. COURAGE was not designed or undertaken to compare "complete" versus "incomplete" revascularization, as investigators and operators were encouraged to perform PCI on the culprit lesion(s) that were deemed to be causing the chronic coronary syndrome. Thus, an important (but as yet unanswered) question is whether clinical outcomes can be favorably influenced by more effective or complete revascularization, particularly in high-risk SIHD patients with left ventricular systolic dysfunction (ejection fraction < 50%) and/or those with moderate to severe myocardial ischemia. Such a randomized trial has recently been proposed to the National Heart, Lung and Blood Institute.

Angina Relief and Improved Quality of Life

Rates of angina were consistently lower in the PCI patients as compared with the medical therapy patients during follow-up, and rates of subsequent revascularization were likewise lower. However, there was a substantial increase in freedom from angina in medically treated patients as well, most of which had taken place by 1 year but with a further improvement to 5 years.[11] To what extent this reflects a benefit of specific antianginal medications (such as nitrates and β-blockers) and to what extent it may reflect an effect of disease-modifying therapies such as statins and inhibitors of the renin-angiotensin system on coronary stenoses is unclear.

In addition, whether PCI can provide an incremental quality of life benefit over OMT in patients with chronic angina due to SIHD was largely unknown until the COURAGE trial was conducted. A comprehensive, prospective assessment of quality of life was imbedded in the trial proper during which angina-specific health status (Seattle Angina Questionnaire [SAQ]) and overall physical and mental function (RAND-36) were assessed at baseline and sequentially during follow-up.[21] Clearly, how patients regard their own health and functioning is critical, and both the SAQ and RAND-36 are patient-reported health outcomes instruments. Based on the SAQ analysis, there was significantly better angina control with PCI for the first 12 to 24 months across the key domains of physical limitation, anginal frequency, and quality of life. Although the differences between treatment arms were statistically significant, the clinical differences were substantially smaller than the within-group benefits noted for both arms. The SAQ data were likewise supported by the RAND-36, which, as a general health questionnaire, showed less consistent benefit of PCI plus OMT, because not all scales on the RAND-36 showed incremental benefit of PCI plus OMT. Somewhat unexpectedly, there was rapid improvement in health status for almost all measures in both groups by 1 to 3 months of follow-up. Importantly, there was significant and rapid improvement in SAQ scores in OMT patients who did *not* cross over to PCI plus OMT. However, the small group of patients who crossed over early from OMT to PCI plus OMT (only 16.5% of OMT patients crossed over during the first year of follow-up) had remarkably low SAQ scores at baseline, and rapid and dramatic improvement in their scores.[21]

What these data indicate is as follows: COURAGE demonstrated that

an initial strategy of PCI added to OMT in patients with stable CAD relieved angina to a greater extent than an initial strategy of OMT alone for a period of approximately 24 months. Because the overall COURAGE trial results did not show that the addition of PCI to OMT reduced cardiovascular events,[11,12] these important quality of life findings[21] permit physicians to engage in an evidence-based discussion with patients about the expected clinical and health status benefits of initial versus deferred PCI when added to OMT. If PCI is deferred, physician and patient alike can be confident that risk of MI or death is not increased. This should foster a patient-centered approach that considers both the incidence of clinical events as well as health-related quality of life to help guide the decision about timing and need for PCI.

Reducing Myocardial Ischemia

A substudy of the COURAGE trial evaluated the effectiveness of PCI as an adjunct to OMT using myocardial perfusion imaging (MPI).[22] Of 2287 patients, 314 underwent MPI before treatment and 6 to 18 months thereafter. At follow-up, the reduction in ischemia was greater with PCI plus OMT than with OMT alone (−2.7% vs −0.5%; $P < .0001$), and more patients in the PCI plus OMT group exhibited a reduction in ischemia of 5% or more (33% vs 19%; $P = .0004$). However, ischemia reduction did not lower the risk of death or MI after adjustment for other baseline inequalities and other relevant covariates. These findings are likewise consistent with those of Mahmarian and colleagues,[23] showing that intensive medical treatment was comparable to revascularization with respect to cardiac events even in high-risk stable postinfarction patients with ischemic perfusion defects; however, both trials were nonrandomized and underpowered for this purpose. Although 2 other trials have reported a reduction in risk (including mortality) using PCI in asymptomatic patients with exercise-induced myocardial ischemia,[24,25] the intensity of medical therapy was not as rigorous as in COURAGE.[11]

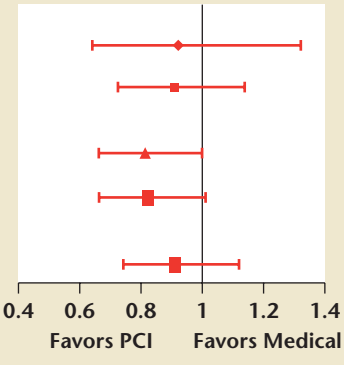
More recently, a meta-analysis by Schömig and colleagues[26] purports to show a significant long-term survival advantage with PCI "in patients with stable coronary artery disease," based on a pooled analysis of 17 randomized trials comparing a PCI-based invasive strategy with medical treatment in 7513 patients. Although the odds ratio for all-cause death was 0.80 (95% CI, 0.64-0.99), indicative of a 20% relative mortality reduction, 5 of the 17 trials included in this so-called meta-analysis were either acute MI trials or post-MI trials. In a follow-up analysis and reinterpretation of the Schömig meta-analysis, Wijeysundera and Ko[27] performed a "corrected meta-analysis" and demonstrated that, after the appropriate removal of these 5 acute or post-MI trials, there was no evidence for a mortality reduction with PCI as compared with OMT—highlighting what they described as an "apples and oranges" comparison (Figure 3).

Clinical Practice Implications

Why is it, then, that PCI reduces death or MI in ACS patients but does not apparently confer the same cardioprotective effect in patients with SIHD patients who, in COURAGE,

Figure 3. *In a follow-up analysis and reinterpretation of the Schömig meta-analysis,[26] Wijeysundera and Ko[27] performed a "corrected meta-analysis" that excluded 5 trials that were either acute MI trials or post-MI trials. After the removal of these 5 trials, there was no evidence for a mortality reduction with percutaneous coronary intervention as compared with optimal medical therapy. CABG, coronary artery bypass grafting; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; MI, myocardial infarction; PCI, percutaneous coronary intervention. Reprinted with permission from Wijeysundera HC, Ko DT. Does percutaneous coronary intervention reduce mortality in patients with stable chronic angina: are we talking about apples and oranges?* Circulation: Cardiovascular Quality and Outcomes. *2009;2:123-126.*[27]

Meta-Analysis	Odds Ratio	95% CI	*P* Value	Deaths PCI	Deaths Medical
Katritsis review[12]	0.94	0.72–1.24	.68	96/1428	101/1424
Katritsis[12] + COURAGE[10,11]	0.91	0.72–1.14	.41	180/2577	196/2562
Schömig review[26]	0.80	0.64–0.99	.05	275/3625	335/3787
Schömig review (without CABG trials)	0.82	0.66–1.01	.07	207/2673	250/2667
Schömig review (without CABG and MI)	0.91	0.74–1.12	.38	194/2407	210/2388



nonetheless exhibited significant myocardial ischemia and extensive multivessel CAD, for which one might anticipate a more durable clinical benefit of PCI over and above mere angina relief? The findings may be explained, in part, by differences in atherosclerotic plaque morphology and vascular remodeling associated with ACS as compared with stable CAD. Vulnerable plaques, precursors of ACS, tend to have thin fibrous caps, large lipid cores, fewer smooth muscle cells, more macrophages, and less collagen, and they are associated with outward (expansive) remodeling of the coronary artery wall, causing less stenosis of the coronary lumen.[1] As a result, vulnerable plaques do not usually cause a significant stenosis prior to rupture and precipitation of an acute coronary syndrome.[1] By contrast, stable plaques tend to have thick fibrous caps, small lipid cores, more smooth muscle cells, fewer macrophages, and more collagen, and they are ultimately associated with inward (constrictive) remodeling that narrows the coronary lumen. These lesions produce ischemia and anginal symptoms and are easily detected by coronary angiography, but they are less likely to result in an acute coronary syndrome.[2,3] Focal management of even severely stenotic coronary lesions with PCI in COURAGE did not reduce death or MI, presumably because these treated stenoses were not likely to trigger an ACS event. Furthermore, our lower than projected event rate in the medical therapy group may be explained by systemic therapy that reduced plaque vulnerability through aggressive, multiple risk factor intervention and evidence-based medication use.

The COURAGE trial therefore provides the best evidence in support of guideline recommendations to the effect that "the majority of patients . . . should be treated medically," and that revascularization is best reserved for patients with objective evidence of ischemia despite ongoing intensive medical therapy.[11] Unfortunately, the guidelines fail to define the appropriate intensity of anti-ischemic medical therapy. In a study of patients with chronic stable angina who were referred for coronary angiography,[28] intensity averaged only 15 on a scale from 0 to 100—equivalent to an average dose of a single antianginal drug—and 15% were not being treated with any antianginal medications. These findings have important implications regarding the management of patients with SIHD and the associated national costs of health care. Quite simply, the erroneous conclusion may be that a large number of patients fail medical therapy when, in fact, those patients never received enough medical therapy to make that determination.

Lastly, it has been argued that the COURAGE trial results apply only to a small fraction of CAD patients, and that the majority of patients who undergo PCI in the United States do so for acute MI, ACS, or unstable angina symptoms. Indeed, in a recent analysis of more than 2.6 million PCI admissions (2005-2007) at 968 US sites in the National Cardiovascular Data Registry,[29] 58% of elective PCI procedures were performed in patients with SIHD; thus, the results of the COURAGE trial would be directly relevant to as many as 700,000 patients annually.

Will Clinical Practice Change?

COURAGE has begun to shift thinking and change clinical practice in the United States, surely as it has already worldwide. Although no one trial is likely to result in profound change, there is reason to believe that COURAGE will reorient our decision-making "set point" away from what has been a largely routine procedural approach to initial patient management for stable CAD. Additionally, the recent results of the Bypass Angioplasty Revascularization Investigation With Diabetes Trial (BARI 2D)[30] in 2368 type 2 diabetes patients replicate the principal finding of the COURAGE trial—that an initial strategy of PCI provides no incremental clinical benefit over intensive medical therapy, and an "OMT-first" instead of a "PCI-first" strategy seems justifiable in many diabetes patients with coronary disease. Among those who remain symptomatic despite intensive treatment, or who have substantial ischemia or extensive coronary artery disease, revascularization is appropriate and either PCI or coronary artery bypass grafting (CABG) is a reasonable choice, depending on the anatomic complexity of disease.

Thus, we now have 2 contemporary randomized trials of OMT versus PCI in more than 4600 SIHD patients[11,30] showing that OMT as an initial management strategy is the equal of PCI. Together with the 11 earlier randomized trials of chronic stable angina patients prior to COURAGE, comprising 2950 patients,[12] we now have outcomes data on 7605 patients from 13 trials supporting the clinical benefit of OMT.

The results of both COURAGE and now BARI 2D emphasize that, over the past 20 years, there have been profound advances in PCI, CABG surgery, and OMT. Is it likely these trial results will change clinical practice? PCI use in the United States remains high (1.2 million procedures/year), and 75% involve DES.[29] As health care reform looms on the horizon, physicians increasingly will need to make informed, evidence-based treatment decisions that improve not only patients' symptoms,

but clinical outcomes as well. Both COURAGE and BARI 2D indicate that, for many patients with SIHD (with or without diabetes), and certainly those with less severe anatomic CAD, OMT rather than any intervention is an excellent first-line strategy. When revascularization is indicated, both BARI 2D and other studies currently support CABG surgery as the preferred approach, whereas PCI may be considered in patients who need revascularization for symptom relief or less extensive anatomic CAD.[31]

Lastly, although the results of any randomized trial must be individualized to specific patients, a "multidisciplinary team approach" to clinical decision-making can ensure that all therapeutic options (OMT, PCI, or CABG) are fully and transparently discussed so that patients are offered the most appropriate evidence-based treatment recommendations. Even leading interventional cardiologists, in the previously-cited authoritative review,[16] stated the following: "This 'convenient' approach to treat what is there [with PCI] has become ingrained and is part of both patients' and physicians' expectations. Nonetheless, the consequence may be the lost opportunity *to discuss all the therapeutic options* [italics added] in a less urgent setting and with all the information at hand."

Conclusion

Simply stated, CAD is a systemic problem that requires systemic treatment. Flow-limiting lesions cause angina and ischemia but may not necessarily be the lesions predisposing to death, MI, and ACS. OMT is directed toward stabilizing so-called vulnerable plaques that are frequently mild angiographically and nonobstructive, such that OMT should rightfully be regarded as the preferred therapeutic approach to reducing clinical events in patients with chronic coronary syndromes and as complementary to focal revascularization approaches directed toward angina and ischemia relief, if needed. Achieving and maintaining multiple treatment targets may be a difficult challenge, but it is well worth the effort.

COURAGE has, indeed, confronted conventional wisdom and an existing belief system that chronic angina, objective evidence of ischemia, and significant obstructive CAD may not inevitably require myocardial revascularization as an initial management strategy. The results are consonant with currently published American College of Cardiology/American Heart Association clinical practice guidelines that OMT should be considered an appropriate and favored first approach in the majority of stable CAD patients. ■

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References

1. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664-1672.
2. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12:56-62.
3. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a

Main Points

- The main findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial indicate that, as an initial management strategy in patients with stable coronary artery disease (CAD), percutaneous coronary intervention (PCI) did not reduce death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy (OMT).
- OMT as used in COURAGE represents a model for secondary prevention in clinical practice.
- COURAGE demonstrated that an initial strategy of PCI added to OMT in patients with stable CAD relieved angina to a greater extent than an initial strategy of OMT alone for a period of approximately 24 months.
- A substudy of the COURAGE trial evaluated the effectiveness of PCI as an adjunct to OMT using myocardial perfusion imaging. The reduction in ischemia was greater with PCI plus OMT than with OMT alone, and more patients in the PCI plus OMT group exhibited a reduction in ischemia of 5% or more.
- The COURAGE trial provides the best evidence in support of guideline recommendations to the effect that most patients should be treated medically and that revascularization is best reserved for patients with objective evidence of ischemia despite ongoing intensive medical therapy.
- A "multidisciplinary team approach" to clinical decision-making can ensure that all therapeutic options (OMT, PCI, or coronary artery bypass grafting) are fully and transparently discussed so that patients are offered the most appropriate evidence-based treatment recommendations.

subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988;78:1157-1166.
4. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation*. 2004;110:588-636.
5. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003; 361:13-20.
6. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet*. 1999;354:708-715.
7. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001; 344:1879-1887.
8. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet*. 2002;360:743-751.
9. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005;293:2908-2917.
10. Boden WE, O'Rourke RA, Teo KK, et al. The evolving pattern of symptomatic coronary artery disease in the United States and Canada: baseline characteristics of the Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation (COURAGE) Trial. *Am J Cardiol*. 2007;99:208-212.
11. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356: 1503-1516.
12. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation*. 2005;111:2906-2912.
13. Boden WE, O'Rourke RA, Teo KK, et al. Impact of optimal medical therapy with or without percutaneous coronary intervention on long-term cardiovascular end points in patients with stable coronary artery disease (from the COURAGE trial). *Am J Cardiol*. 2009;104:1-4.
14. Kereiakes DJ, Teirstein PS, Sarembock IJ, et al. The truth and consequences of the COURAGE trial. *J Am Coll Cardiol*. 2007;50:1598-1603.
15. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcomes in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol*. 2003;42:1161-1170.
16. Holmes DR Jr, Gersh BJ, Whitlow P, et al. Percutaneous coronary intervention for chronic stable angina: a reassessment. *JACC Cardiovasc Interv*. 2008;1:34-43.
17. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med*. 2003;138:777-786.
18. Babapulle MN, Joseph L, Bélisle P, et al. A hierarchical Bayesian meta-analysis of randomized clinical trials of drug-eluting stents. *Lancet*. 2004;364:583-591.
19. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370:937-948.
20. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, et al. Percutaneous coronary interventions for non-acute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. *Lancet*. 2009;373:911-918.
21. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359: 677-687.
22. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden. Results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283-1291.
23. Mahmarian JJ, Dakik HA, Filipchuk NG, et al. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction. *J Am Coll Cardiol*. 2006;48: 2458-2467.
24. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation*. 1997; 95:2037-2043.
25. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. *JAMA*. 2007;297:1985-1991.
26. Schömig A, Mehilli J, de Waha A, et al. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention–based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:894-904.
27. Wijeysundera HC, Ko DT. Does percutaneous coronary intervention reduce mortality in patients with stable chronic angina: are we talking about apples and oranges? *Circulation: Cardiovascular Quality and Outcomes*. 2009;2: 123-126.
28. Samuels BA, Diamond GA, Mahrer PR, Denton TA. Intensity of antianginal therapy in patients referred for coronary angiography: a comparison of fee-for-service and health maintenance organization therapeutic strategies. *Clin Cardiol*. 2000;23:165-170.
29. *ACC NCDR Data*. Durham, NC: Duke Clinical Research Institute; 2009.
30. BARI 2D Study Group, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503-2515.
31. Boden WE, Taggart DP. Diabetes and coronary disease: a moving target amid evolving therapies? *N Engl J Med*. 2009;360:2570-2572.