CORRESPONDENCE

PCI for Stable Coronary Disease

TO THE EDITOR: On the basis of the report by Boden et al. on the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (April 12 issue),[1] we updated our meta-analysis of percutaneous coronary intervention (PCI) versus medical treatment in nonacute coronary artery disease.[2] The calculations reinforce the absence of a difference between PCI and medical therapy in patients with stable coronary artery disease, with 95% confidence intervals excluding a 12% reduction in the relative risk of death from cardiac causes or myocardial infarction with PCI (Table 1).

The guidelines of the European Society of Cardiology,[3] which were published at the same time as our initial meta-analysis, strongly supported the use of PCI in clinically stable patients, focusing on the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial.[4] However, since the intervention group in the ACIP trial underwent PCI or bypass surgery, it was impossible to distinguish benefits due specifically to PCI. The guidelines of the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions, which were published a year later,[5] still recommended PCI for asymptomatic patients with ischemia. Unfortunately, meta-analyses show particular difficulty in overcoming tradition when the evidence suggests abandoning a large share of the most common procedure of a medical specialty.[6] Will the latest evidence now lead to changes in the recommendations and clinical practice?

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Table 1. Update of Meta-Analysis of PCI, as Compared with Medical Treatment, for Stable Coronary Artery Disease.*

Outcome	PCI	Medical Treatment	Summary Risk Ratio (95% CI)	P Value	Q Statistic
		no.			
Death from any cause	195	219	0.90 (0.75–1.08)	0.25	5.93
Myocardial infarction or death from cardiac causes	321	313	1.01 (0.88–1.17)	0.87	10.35
Nonfatal myocardial infarction	242	221	1.07 (0.90–1.28)	0.43	8.75

* The updated meta-analysis includes 13 studies involving 5442 patients. The original meta-analysis[2] included data from 11 trials. The updated meta-analysis includes data from the COURAGE trial and the Adenosine Sestamibi SPECT Post-Infarction Evaluation (INSPIRE) trial and updated long-term follow-up data from the Medicine, Angioplasty, or Surgery Study II (MASS II). Summary risk ratios by fixed and random effects were practically identical in the two groups, since there was no between-study heterogeneity for any of the three outcomes ($I^2=0$). PCI denotes percutaneous coronary intervention.

TO THE EDITOR: In the COURAGE trial, Boden et al. reaffirm that PCI does not reduce the risk of death or myocardial infarction among patients with stable coronary disease. But the authors mistakenly state that "approximately 85% of all PCI procedures are undertaken electively." This statement misinterprets the cited report by Feldman et al.,[1] which explicitly counted PCI procedures in patients with unstable angina as "elective" (Table 2 of the report by Feldman et al.). On the basis of data in Tables 1 and 2 of that report, of 82,140 patients who underwent PCI, 10,964 underwent "emergency" procedures and 45,459 had "unstable angina." This leaves 25,717 patients with stable condition who underwent elective procedures (31% rather than the 85% reported by Boden et al.). Moreover, of the 31% of patients who underwent elective procedures, many probably had criteria that would have excluded them from the COURAGE trial: class IV angina, a markedly positive exercise test, refractory heart failure, poor ventricular function, or recent revascularization. Therefore, important as the results of the COURAGE trial are, it must be recognized that they reflect the findings in only a small minority of patients with coronary disease, mostly with mild symptoms (a median of three episodes of angina per week), one third of whom ultimately required revascularization within a median of 10 months.

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1. Feldman DN, Gade CL, Slotwiner AJ, et al. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). Am J Cardiol 2006;98:1334-9.

TO THE EDITOR: Boden et al. conclude that medical therapy alone is as effective as PCI in reducing the incidence of major cardiovascular events. However, issues of patient-selection bias and PCI methodology weaken these conclusions.

First, the authors excluded more than 90% of the patients who were evaluated, suggesting a highly selected study population. Of those patients, 6554 — about three times the reported study size — were excluded for "logistic reasons," with no further explanation.

Among the patients who underwent PCI, 14.5% of the lesions were treated with coronary angioplasty without placement of a stent, a procedure that is subject to rates of revascularization and periprocedural myocardial infarction that are higher than those among patients receiving stents.[1] No mention is made about the use of glycoprotein IIb/IIIa inhibitors, medications that have been shown to reduce the risk of myocardial infarction.[2,3] Medical therapy may be equivalent to PCI for stable coronary artery disease, but further studies, including trials involving the use of drug-eluting stents, are warranted.

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in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
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TO THE EDITOR: Although two thirds of patients in the COURAGE trial had multivessel disease, 59% received only one stent when treated with PCI, suggesting that revascularization was incomplete in most cases. In a recent report on data from the New York State PCI Registry,[1] incomplete revascularization was recognized as a powerful independent predictor of mortality and need for subsequent revascularization. Boden et al. should state the rate of incomplete revascularization in the PCI group of the COURAGE trial. It would also be important to know whether patients who were treated in non–Veterans Affairs centers in the United States, among whom the event rate was 6 percentage points lower in the PCI group than in the medical-therapy group, underwent complete revascularization more frequently than did patients who were treated in Canadian or U.S. Veterans Affairs centers, among whom PCI did not provide any advantage.

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TO THE EDITOR: Although Boden et al. report the prognostic equipotency of medical therapy with or without PCI among patients with stable coronary artery disease, they did not stratify patients according to the ischemic burden. The ischemic burden that is shown on noninvasive imaging studies, such as radionuclide myocardial perfusion imaging (MPI), correlates with the cardiac event rate and confers superior prognostic power, as compared with information from coronary angiography.[1]

Among patients with ischemia as seen on MPI, PCI or coronary bypass surgery has been shown to improve the outcome, as compared with medical therapy.[2,3] Conversely, the prevailing literature attests to better prognosis without intervention among patients who do not have ischemia on MPI.[4]

The magnitude of the ischemic burden is a set of quantifiable information obtained by means of stress echocardiography or MPI in the majority of patients in the study by Boden et al. These data should be used in the analysis of treatment efficacy in the COURAGE trial.

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TO THE EDITOR: Boden et al. appropriately analyze their data according to the intention-to-treat principle. However, in the medical-therapy group, 25.5% of patients (32.6% who underwent revascularization minus 7.1% who underwent coronary-artery bypass grafting) underwent PCI by the end of the study for refractory angina or worsening ischemia on noninvasive testing. Moreover, in 4% of the patients in the PCI group, PCI was not attempted. Outcome data for the 848 patients in the medical-therapy group who did not undergo subsequent PCI (74.5%) were not reported separately. Hence, the effect of subsequent PCI on the outcome in the medical-therapy group is unknown. Specifically, calculation of the prevalence of angina needs to take subsequent PCI into account, since PCI was performed for refractory angina. Because of the high rate of crossover, analyzing the data separately according to the

treatment actually received would be useful in interpreting the trial results.

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TO THE EDITOR: Boden et al. state that "patients undergoing PCI received aspirin and clopidogrel, in accordance with accepted treatment guidelines and established practice standards," without specifying the duration of treatment with clopidogrel among those who received coronary stents. In the Clopidogrel for the Reduction of Events during Observation (CREDO) study,[1] the reported 1-year incidence of death, myocardial infarction, or stroke was 26.9% lower among patients treated with dual antiplatelet agents for 1 year than among those treated for only 1 month. In the COURAGE study, among patients with this composite end point, 222 were in the PCI group and 213 were in the medical-therapy group. If these patients were treated with dual antiplatelet agents for only 1 month, extending the duration of therapy to 1 year might have prevented another 60 deaths, myocardial infarctions, or strokes in the PCI group. This benefit would translate to a relative risk reduction of about 29% (odds ratio, 0.71; 95% confidence interval, 0.57 to 0.89; P=0.003).

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THE AUTHORS REPLY: With respect to the updated meta-analysis by Katritsis and Ioannidis: it is unlikely that we missed any treatment benefit in favor of PCI in our trial. The clinical guidelines of the American College of Cardiology and the American Heart Association[1] advocate intensive medical therapy with lifestyle and pharmacologic interventions as the initial approach. Contemporary cardiologists increasingly favor procedurally driven management. The results of our trial should encourage more thoughtful discussion between patients and doctors regarding the risks and benefits of, need for, and timing of revascularization. Our findings should also inspire confidence among physicians that they will not subject clinically stable patients to increased risk by deferring initial PCI.

Wharton et al. challenge our statement that most PCI procedures in the United States are elective. Although the clarification they offer regarding "elective" PCI is appreciated, data from the National Cardiovascular Data Registry indicate that approximately 50% of PCI procedures are truly elective, as opposed to urgent or emergent (Rumsfeld J: personal communication). Furthermore, the patients in our trial did not have mostly "mild symptoms" — 58% had Canadian Cardiovascular Society class II or III angina — and the statement by Wharton et al. that one third of patients "ultimately required revascularization within a median of 10 months" is not correct. Rather, the median time to revascularization was 10 months, and only 16% of patients underwent revascularization within 10 months.

We dispute the arguments by Shah et al. that "patient-selection bias" and "PCI methodology" weaken our conclusion that optimal medical therapy is as effective as PCI plus medical therapy. We included sufficiently high-risk patients to test our hypothesis that PCI plus medical therapy would be superior. Although our screening process was not efficient, our inclusion criteria were rigorous and included the presence of a major coronary stenosis on angiography and objective evidence of ischemia. These requirements resulted in a study population that was representative of the majority of patients with stable coronary artery disease. Regarding PCI, the proportion of stent use in our study reflects current practice. Glycoprotein IIb/IIIa agents were used in accordance with established practice. A censored analysis that excluded periprocedural myocardial infarction showed no difference in overall rates of myocardial infarction between groups for the primary end point. Further analyses from our trial will explore whether these glycoprotein IIb/IIIa agents were associated with lower periprocedural rates of myocardial infarction.

Investigators in our trial were encouraged to "perform complete revascularization as clinically appropriate." De Servi implicates "incomplete revascularization" in explaining the results in the PCI group. This simplistic assessment of revascularization does not take into consideration

previous myocardial infarction, bypass grafting, and other factors.

As suggested by Kiat, we are performing post hoc analyses to better delineate a high-risk subgroup on the basis of the ischemic burden as assessed on MPI at baseline and during a follow-up period of 6 to 14 months.

Nagajothi et al. acknowledge that our intention-to-treat analysis was appropriate but encourage further analysis according to actual treatment received. A detailed analysis of the "crossover" population is under way.

Finally, Mak emphasizes the incremental benefit of the use of dual antiplatelet therapy on the composite end point of death, myocardial infarction, or stroke at 1 year in the CREDO trial.[2] Enrollment in our trial antedated these results. However, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial,[3] involving patients with stable coronary artery disease, did not show a compelling benefit of combined treatment with aspirin and clopidogrel in reducing death, myocardial infarction, or stroke in long-term follow-up.

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Diabetic Gastroparesis

TO THE EDITOR: In his review of diabetic gastroparesis, Camilleri (Feb. 22 issue)[1] states that in our clinical trial of exenatide,[2] nausea and vomiting led to the "cessation of treatment in about one third of patients." This information is incorrect. Of 282 patients randomly assigned to receive exenatide, 54 withdrew from the study (27 withdrew because of an adverse event, 10 because of protocol violations, 7 because of the patient's decision, 4 because of loss of glucose control, and 1 because of the physician's decision, and 5 were lost to follow-up). As stated in our article, 18 of these patients withdrew from the study because of nausea or other gastrointestinal symptoms. This rate is in line with the dropout rates in other recent clinical trials, which range from 1.8 to 5.1%.[3-5] Mild-to-moderate nausea is the most common adverse event in patients receiving exenatide. However, the development of tolerance to these adverse gastrointestinal effects of exenatide has been suggested in our trial as well as in other long-term phase 3 trials of the drug that have been reported.[3-5]

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TO THE EDITOR: In Table 2 of his article, Camilleri lists the motilin-receptor agonists erythromycin,