When Is Better Not Good Enough? 
Insights From the COURAGE Economic Study 
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More than 800 000 percutaneous coronary intervention (PCI) procedures are performed annually in the United States alone at a cost of more than $10 billion. Although many of these procedures are performed on patients with symptoms such as acute myocardial infarction and unstable angina, for whom randomized clinical trials have demonstrated substantial benefits including prevention of myocardial infarction and reduced mortality rate,1,2 approximately half of all PCI procedures are performed on patients with stable coronary artery disease. In this setting, PCI has been shown to improve anginal symptoms and quality of life; however, it has not significantly affected clinical outcomes such as death and nonfatal myocardial infarction in prior randomized trials.3,4 Given the substantial economic burden of these procedures and the modest clinical benefits to patients with stable coronary artery disease, it is therefore not surprising that PCI—and particularly, elective PCI for stable patients—is a prime target for economic evaluation.

As such, the article by Weintraub et al5 in this issue of Circulation: Cardiovascular Quality and Outcomes, which describes the results of a prospective in-trial and lifetime cost–utility analysis performed alongside the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluations) trial, is a welcome addition to the cardiovascular literature. COURAGE was a randomized clinical trial that compared PCI with optimal medical therapy (PCI+OMT) versus OMT alone as initial management strategies for patients with stable coronary artery disease. As previously described, at a median follow-up of 4.6 years, there were no significant differences between the 2 treatment arms with respect to the primary end point of all-cause death or myocardial infarction.4 On the other hand, initial PCI did provide modest benefits in terms of more rapid and complete relief of angina as well as improved quality of life.6 Although these benefits were attenuated beyond the first 2 years of follow-up, it is important to note that approximately one third of patients randomized to OMT alone ultimately underwent subsequent PCI during this period.

In the prespecified cost-effectiveness analysis, cardiovascular resource utilization (including inpatient and outpatient services and medications) was assessed prospectively from the trial population, and costs were assessed from the standpoint of the US healthcare system (largely using Medicare reimbursement rates as a proxy for cost). Quality of life was assessed directly from each study participant in terms of “utility” weights, which are values that reflect each patient’s preference for his or her health state relative to the extremes of perfect health (utility = 1) and death (utility = 0).

The main findings of the study were that during the observed follow-up period (a median of 4.6 years), total in-trial costs were $34 843 for the PCI+OMT group and $24 718 for the OMT group with in-trial quality-adjusted life expectancies of 3.56 and 3.51 quality-adjusted life years (QALYs), respectively. The within-trial cost-effectiveness ratio, which is the difference in cost divided by the difference in quality-adjusted life expectancy, was thus $206 229/QALY gained with PCI+OMT compared to OMT alone. When the in-trial event data were used to project lifetime costs, utilities, and life expectancies, these values changed only minimally, and the lifetime cost-effectiveness ratio was $168 019/QALY gained for initial PCI. Bootstrap analysis demonstrated that the cost–utility ratio remained >$50 000/QALY in 89.9% of trial replicates and >$100 000/QALY in 64.6% of trial replicates. Although no single cost-effectiveness threshold is universally accepted within the US healthcare system, the general consensus is that ratios <20 000 per year of life gained are highly attractive, whereas ratios between $20 000 and $50 000 per year of life gained are reasonably attractive.7,8 On the basis of these findings, Weintraub et al suggest that the use of PCI to treat chronic stable coronary artery disease is not an economically attractive strategy in the current healthcare environment.

Given the overall results of COURAGE, the results of the economic analysis are not particularly surprising. The improvement in overall quality-adjusted life expectancy was modest at best because there were no differences in hard outcomes (which might be expected to translate into substantial gains in life expectancy for the trial population), and the quality-of-life benefits that were observed were transient. The finding that treatment costs were substantially higher with PCI is also fairly intuitive given the high up-front costs of the PCI procedures. On the other hand, it is somewhat surprising that PCI did not result in substantial reductions in follow-up cost. Indeed, over the ~5-year follow-up period, “downstream” costs were only $1285/patient lower with initial PCI+OMT versus with OMT alone, which translates to a...
savings of <$300/patient per year. These findings reflect that there were no differences in the incidence of bypass surgery during follow-up and there were also limited reductions in the need for subsequent PCI procedures in the initial PCI group.

One important consideration in interpreting the COURAGE results is whether they apply to contemporary practice in which the majority of PCI procedures involve placement of one or more drug-eluting stents (DES). Although DES were used in <5% of PCI procedures in COURAGE, it appears unlikely that their use in even 100% of the study population would have significantly affected the overall results. To address these important concerns, the COURAGE investigators included a sensitivity analysis that incorporated both the proven benefits of DES (ie, a reduction in the need for subsequent revascularization procedures) and the costs (ie, higher procedural and medication-related costs for extended dual-antiplatelet therapy). Although the cost-effectiveness of PCI was improved in this hypothetical scenario, the resulting cost–utility ratio was still >$150 000/QALY in both in-trial and lifetime analyses. Once again, these results are not surprising, since DES have not been shown in randomized trials to either lower costs10,11 or improve survival.12 Although the authors did not explicitly consider any quality-of-life benefits associated with DES (which have been estimated to be ≈0.01 to 0.02 QALYs),10 it is clear that even had they incorporated these benefits, the resulting cost–utility ratio would still have remained in the unfavorable range.

The economic evaluation of COURAGE by Weintraub et al is not without limitations, however. The assessment of health-state utilities was performed with a method called the standard gamble, which attempts to assess patients’ preferences for their health in the hypothetical scenario of being restored to “perfect health.” Recently published guidelines from the US Panel on Cost-Effectiveness in Health and Medicine strongly recommend the use of utility weights derived from the general community of “potential patients” rather than from the subjects themselves, however.13 Because patients may adapt to their condition over time (particularly when the condition is chronic), they may actually understate its impact on their quality of life, thus leading to underestimation of the quality-of-life benefits associated with an effective treatment. An additional limitation of the study is its failure to include the cost of diagnostic coronary angiography in the OMT arm. Although it is technically correct that randomization occurred after coronary angiography in COURAGE, the costs of diagnostic angiography are already incorporated in the PCI + OMT group (as part of the PCI procedure). It would have thus been appropriate to incorporate the costs of angiography in the OMT group as well, because the selection of appropriate patients for the trial was partly based on this information. Whether inclusion of these costs would have substantially altered the study’s results is unknown.

The most important limitation of the COURAGE economic study, however, is that it is based on the results of the COURAGE trial itself, which may limit the generalizability of the study’s conclusions. Although the inclusion criteria for COURAGE were broad and would be expected to encompass a large proportion of the patients who undergo elective PCI, there are reasons to believe that the actual population enrolled in the trial was quite different. Like other randomized trials of entrenched therapies, COURAGE had difficulty with recruitment, ultimately enrolling <10% of patients who were screened for the trial over a significantly longer period of enrollment than was originally projected. Less than 20% of patients were enrolled in non–Veterans Administration hospitals within the United States. The compliance with OMT in the trial was far in excess of that reported in other population-based studies of less-selected patients,14 suggesting that patients within the trial may have been ideal candidates for OMT. These factors alone should give one pause before generalizing the cost-effectiveness of PCI as derived from this trial to more broadly representative populations.

Finally, the slow recruitment for the trial may be an indication that the COURAGE investigators were challenged to randomize patients with extremely severe stenoses supplying major epicardial vessels (eg, 95% stenosis of a proximal left anterior descending artery) or specific patients for whom it was anticipated that withholding PCI was unlikely to be a successful strategy (eg, patients with more severe or progressive symptoms that would be difficult to control without revascularization). On the basis of the Canadian Cardiovascular Society’s angina classification scale, 42% of patients enrolled in the trial had either mild angina or no anginal symptoms. Additionally, the median duration of angina for enrolled patients was 5 months. This suggests a population of patients with very stable angina overall, as the majority of patients could afford to wait several months for randomized treatment in the study.

It could be hypothesized that patients with more severe symptoms or with stenoses, whom investigators a priori might have judged to be difficult to manage medically, would derive substantially greater quality-of-life benefits from revascularization than were observed on average in the COURAGE population. For such patients, the cost-effectiveness of PCI would likely differ substantially from that observed in COURAGE. In addition, aside from improvements in quality of life with PCI, for patients with extensive ischemia and/or multivessel disease, there may still be a role for PCI in improving long-term prognosis.15–17 Although COURAGE did include patients with both of these clinical features, the annualized rate of cardiac death through the follow-up period was ≈0.4% to 0.5%/year (or possibly as high as 1%/year if deaths due to unknown causes are attributed to cardiovascular disease), which is a low overall rate compared with less-selected populations undergoing PCI.18 Thus, the power of the study to demonstrate meaningful differences in long-term mortality rate was markedly diminished. Although it would be possible, in theory, to use the COURAGE data to examine the cost-effectiveness of PCI in high-risk patient subsets, in practice, such subgroup analyses are subject to considerable uncertainty because of the limited sample size and are rarely conclusive (or even informative).

The natural question that arises from the study by Weintraub et al is whether, on the basis of these results, we should stop performing (or paying for) elective PCI in stable patients. Alternatively, it could be proposed that elective PCI would remain a covered service with a mandatory “waiting period” to allow the benefits of medical therapy to become manifest. Although these approaches may be tempting to those who wish to control costs, it is important to consider that just as individual patient-based recommendations exist within a societal context,
individual studies such as COURAGE also exist within a more global context of patients with varying extents of coronary artery disease. In short, these results, like those of any randomized clinical trial, pertain specifically to the population enrolled in the study. Before these data are used to make broad policy decisions, it is critical to establish the characteristics and outcomes of patients enrolled in the trial to assess the overall generalizability of the findings to populations not enrolled in the clinical trial.

Ultimately, most physicians will shun an all-or-none approach, and instead choose to individualize recommendations on a per-patient basis. In this regard, the analysis by Weintraub et al is informative, as it suggests that a strategy of up-front PCI (as opposed to an initial trial of aggressive medical therapy) may be relatively costly given the benefits for selected patients who are similar to those enrolled in COURAGE. Thus, when a procedure that predominantly reduces symptoms in low-risk patients is used, it is important to consider the degree to which symptom relief will affect the patient’s overall sense of well-being. If the amount of relief will be substantial, there are clear societal precedents for supporting elective PCI for such patients. If not, it is difficult to justify the procedure without an adequate attempt at symptom control via medical means.

Finally, it is important to keep in mind that without changes in medical guidelines and insurance-coverage policies, all of these points may be moot. In the present US healthcare environment, it is unclear whether insurers would be willing to restrict access to a procedure that is clearly beneficial purely on the basis of cost-effectiveness. In the absence of such guidelines or restrictions, the physician’s primary responsibility remains to his or her individual patient (and not to society, the Centers for Medicare and Medicaid Services, or a third-party payer). As such, the fact that PCI led to significantly greater and more rapid improvement in angina and quality of life with no excess of complications mandates that physicians should continue to provide PCI to patients when informed of the true risks and benefits of the procedure, request that it be performed for symptomatic relief.

Disclosures
Dr Kirtane is a consultant/advisor to Medtronic Vascular and Abbott Vascular, and receives lecture fees/honoraria from Medtronic Vascular, Abbott Vascular, and Boston Scientific, Inc. Dr Cohen receives grant support from Cordis, Inc and Boston Scientific, Inc, and is a consultant/advisor to Medtronic Vascular.

References

Key Words: Editorials ▪ cost–benefit analysis ▪ epidemiology ▪ angioplasty ▪ transluminal percutaneous
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Circ Cardiovasc Qual Outcomes. 2008;1:4-6
doi: 10.1161/CIRCOUTCOMES.108.814244
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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