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,\textsuperscript{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.\textsuperscript{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 al\textsuperscript{5} 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.\textsuperscript{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.\textsuperscript{5} 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.\textsuperscript{7,8} On the basis of these findings, Weintraub et al\textsuperscript{5} 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 costs or improve survival.

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), 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 state by allowing them to consider what risk of death they would be willing to assume in order to be 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. Because patients may adapt to their condition over time (particularly when the condition is chronic), they may actually underestimate 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, suggesting that patients within the trial may have been ideal candidates for OMT. These facts 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. 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. 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 ap-
proach, and instead choose to individualize recommendations
on a per-patient basis. In this regard, the analysis by Weint-
raub 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 poli-
cies, 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 who, when informed of the true risks and benefits of
the procedure, request that it be performed for symptomatic
relief.

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References
1. Mehta SR, Cannon CP, Fox KAA, Wallentin L, Boden WE, Spacek R,
Widimsky P, McCullough PA, Hunt D, Braunwald E, Yusuf S. Routine
vs selective invasive strategies in patients with acute coronary syndromes:
a collaborative meta-analysis of randomized trials. JAMA. 2005;293:
2908–2917.
2. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intra-
venous thrombolytic therapy for acute myocardial infarction: a quantita-
3. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus
conservative therapy in nonacute coronary artery disease: a meta-analysis.
4. Boden WE, O’Rourke RA, Teo KK, Hartigan PM, Marion DJ, Kostuk WJ,
Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L,
ER, Speruts JA, Berman DS, Mancini GB, Weintraub WS. Optimal
medical therapy with or without PCI for stable coronary disease. N Engl
Hartigan P, Veledar E, Jurkowitz C, Bowen J, Marion DJ, O’Rourke R,
Dada M, Teo KK, Goeree R, Barnett PG. Cost-effectiveness of percuta-
neous coronary intervention in optimally treated stable coronary patients.
Zhang W, Hartigan PM, Lewis C, Veledar E, Bowen J, Dunbar SB,
Deaton C, Kaufman S, O’Rourke RA, Goeree R, Barnett PG, Teo KK,
Boden WE. Effect of PCI on quality of life in patients with stable
7. Goldman L, Gordon DJ, Rifkind BM, Hulley SB, Detsky AS, Goodman
DW, Kiosonas B, Weinstein MC. Cost and health implications of cho-
8. Mark DB, Hlatky MA. Medical economics and the assessment of value in
Vlachos HA, Wilensky RL, Williams DO. Unrestricted use of drug-
eluting stents compared with bare-metal stents in routine clinical practice:
findings from the National Heart, Lung, and Blood Institute Dynamic
of sirolimus-eluting stents for treatment of complex coronary stenoses:
results from the Sirolimus-Eluting Balloon Expandable Stent in the
Treatment of Patients With De Novo Native Coronary Artery Lesions
BJ, Clark MA, Lacey MJ, Russell ME, Ellis SG, Hermiller JB, Cox DA,
Cohen DJ. Cost effectiveness of paclitaxel-eluting stents for patients
undergoing percutaneous coronary revascularization: results from the
12. Stone GW, Moses JW, Ellis SG, Schofer J, Dowskins KD, Morrice M-C,
Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M,
Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and
adherence with cardiovascular drug regimens. Am J Heart. 2006;151:
185–191.
15. Shaw LJ, Berman DS, Marion DJ, Mancini GB, Hayes SW, Hartigan PM,
Weintraub WS, O’Rourke RA, Dada M, Speruts JA, Chaitman BR,
Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P,
Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCal-
listter B, Teo KK, Boden WE. 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.
16. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV,
Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic
review: the comparative effectiveness of percutaneous coronary inter-
2007;147:703–716.
van’t Veer M, Bar F, Hoornije J, Koolen J, Wijnis W, de Bruyne B.
Percutaneous coronary intervention of functionally nonsignificant steno-
sis: 5-year follow-up of the DEFER study. J Am Coll Cardiol. 2007;49:
2105–2111.
R, Maresta A. Long-term safety and efficacy of drug-eluting stents:
two-year results of the REAL (REgistro Angioplastiche dell'Emilia

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