The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial showed that coronary interventional procedures added little to optimal medical therapy with respect to the long-term outcome of patients with stable coronary disease when used as initial therapy. Detractors opine that: 1) the trial was unrealistic in design and the findings were not unexpected; 2) the use of coronary interventional procedures was suboptimal; and 3) the results of COURAGE are not applicable to current clinical practice. We herein reevaluate the evidence with regard to each of these points, and conclude that COURAGE indeed provides relevant new information to assist the practitioner in the appropriate management of patients with stable coronary disease (J Am Coll Cardiol 2007;50:1604–9) © 2007 by the American College of Cardiology Foundation.

According to Schopenhauer (1), truth passes through 3 stages: “First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.” Kereiakes et al. (2) reverse this journey in their review of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial and its conclusion that percutaneous coronary intervention (PCI) adds little to optimal medical therapy (OMT) in the management of stable coronary disease (3). In the present counterpoint, we revisit each signpost and proffer a more optimistic view of the landscape.

Stage 3: “it is ...self-evident”

Point. Kereiakes et al. (2) claim that the COURAGE trial was “neither surprising nor new” compared with previous studies (4). Given what was already known, “COURAGE set an unrealistic goal” by enrolling a small select group of relatively low-risk patients and seeking to detect a large reduction in death or myocardial infarction (MI). Instead, “a noninferiority trial design may have been more appropriate” (2).

Counterpoint. In fact, enrollment criteria in the COURAGE trial were entirely conventional. Clinical equipoise and the usual desiderata of trial design necessitated exclusions at both extremes of risk (serious comorbidity and New York Heart Association (NYHA) functional class IV angina at the high end versus undocumented ischemia and <70% stenosis at the low end), thereby assuring a homogeneous, albeit small, study population (6.4% of 35,539 candidates in the COURAGE trial versus 2.9% of 20,769 candidates in the MASS [Medicine, Angioplasty, or Surgery Study]-II trial [5]).

The COURAGE trial was conceived in 1996, and at the time of its design in 1999, 6 trials comprising 1,872 patients with stable coronary disease had already been published (4). The rate of death or MI was 7.2% for medical therapy versus 8.6% for PCI (20% more) over 6 to 57 months. The COURAGE trial relied instead on a consensus that PCI would perform as well in stable coronary disease as it was thought to do in acute coronary syndromes (W.S. Weintraub, personal communication, June 29, 2007), and its consequent expectation of a 22% risk reduction over 3 years (6) was indeed “unrealistic” (2). Two contemporary meta-analyses (7,8) confirm the benefit of PCI in acute coronary syndromes (Table 1), although a similar meta-analysis (exclusive of the COURAGE trial) shows no comparable benefit in stable coronary disease (Table 2). In this context, the findings in the COURAGE trial are indeed not “new” (2).

But there is more to the story. Table 3 updates Table 2 with the data from the COURAGE trial relative to the hypothesis that PCI+OMT improves death or MI better than OMT in stable coronary disease, thereby circumventing any post hoc considerations of statistical power and assessing the actual observations without regard for what might have been observed (9). Independent of any “unrealistic” expectations, OMT is favored by a ratio of nearly 7:1.

Nevertheless, because the lay public is unlikely to distinguish between unstable and stable disease, most patients undergoing elective PCI often do so under the belief that it indeed prolongs their life or prevents a heart attack. The fact that most (10) of these procedures are performed electively—often in stable patients immediately following ad
of angiographic laboratory” (6). Even if it had not, it is hard to imagine how this would impact angiographic or clinical outcomes as implied (2). For obvious reasons, physicians responsible for day-to-day care cannot wait for post hoc readings. But if PCI were the implications for the typical hospital performing these procedures on an ad hoc basis (12)?

**Stage 2: “it is violently opposed”**

**Point.** Kereiakes et al. (2) contend that PCI was not optimally performed in the COURAGE trial. They argue that if: 1) a core laboratory had assessed the angiographic findings; 2) more patients had been treated in non-Veterans Affairs (VA) hospitals; 3) crossovers had been less; 4) the study had been limited to high-risk patients; 5) the definition of periprocedural MI had been more forgiving; and 6) drug-eluting stents (DES) had been used more freely—then the outcomes and conclusions would have been different. Let us take up each of these points in turn.

**Counterpoint.** By all accounts, the standard of performance in COURAGE was high. The 21% rate of “additional revascularization” (3) is actually less than in ARTS (Arterial Revascularization Therapies Study; 23%) and the MASS-II trial (32%) over comparable follow-up (5,21), and its median of 10 months indicates that about one-half these events occurred in the first year. If, as is likely, this is a consequence of restenosis, it is less than that of bare-metal stenting (22). Moreover, although only one-half of the patients with multivessel disease received multiple stents, this too is comparable to the MASS-II trial (5) and higher than in the New York State Angioplasty Registry (23). Finally, although bypass surgery clearly provides more complete revascularization than PCI, it does not prevent more death or MI (5,21,24).

The design of the COURAGE trial specifically calls for all angiograms being “read centrally by a core angiographic laboratory” (6). Even if it had not, it is hard to imagine how this would impact angiographic or clinical outcomes as implied (2). For obvious reasons, physicians responsible for day-to-day care cannot wait for post hoc readings. But if this were necessary to the effectiveness of PCI, what would be the implications for the typical hospital performing these procedures on an ad hoc basis (12)?
Although sample size restrictions limit the reliability of subgroup analyses, there are no significant differences in outcome between VA and non-VA systems ($p = 0.19$). There is therefore no reason to believe that the observed site-to-site variability differs from that in actual community practice.

Crossover in the COURAGE trial was similar to other revascularization trials. In the surgery trials, crossover ranged from 24% to 30% over 5 to 11 years (25–27) versus 35% over 7 years in RITA (Randomized Intervention Trial of Angina)-2 (28) and 24% over 5 years in the MASS-II trial (5). These high rates are simply a manifestation of the progressive nature of the disease, and very likely represent the exercise of good clinical judgment. In any event, intention-to-treat analysis, by maintaining the advantages of randomization, is unaffected by crossover (29).

Kereiakes et al. (2) imagine that the skewed distribution of anginal frequency in the COURAGE trial “implies...2 patient populations” (1 at high risk and 1 at low risk), which biased the conclusions against PCI (30,31). In fact, there is nothing suspicious about this pattern. If anginal frequency is log normally distributed (32), a single population fully accounts for these observations (Fig. 1). Thus, subgroup analyses reveal no treatment differences between NYHA functional class 0 to I angina versus NYHA functional class II to III angina.

The contrary “premise” that the COURAGE trial comprised a low-risk population, based solely on a cardiac mortality of 0.4% per year (subject to ascertainment error), is contradicted by the magnitude of comorbidity, frequency of inducible ischemia, and prevalence of multivessel disease. In fact, the all-cause mortality of nearly 8% is similar to that in the ARTS trial (21), and death or MI at 5 years is virtually identical to that in acute coronary syndrome trials (33,34). This is not a low-risk population.

The supposition that the definition of myocardial enzyme elevation “no doubt, disadvantaged PCI” compared with OMT (2) is unsupported by the evidence. Only 26 periprocedural MIs occurred using this definition, and a censored analysis that excluded these events did not shift the results in favor of PCI, with a hazard ratio of 0.90 (95% confidence interval 0.73 to 1.10; $p = 0.29$).

Finally, because DES were used infrequently in the COURAGE trial, Kereiakes et al. (2) say this too biased the outcomes against PCI. To explore this possibility, we performed a putative placebo analysis (20). The resultant risk ratio for PCI+OMT versus OMT increased nonsignificantly (Fig. 2), indicating that greater use of DES, if anything, would have been associated with a slightly greater risk of death or MI. The claim that DES would have improved angina-free status and quality of life (albeit likely) remains conjectural.

**Stage 1: “it is ridiculed”**

**Point.** Kereiakes et al. (2) question the relevance of the COURAGE trial to clinical practice, because “the vast majority of Americans [already] receive medical therapy for their coronary artery disease.” However, they then note that the quality of medical therapy in the COURAGE trial is not achievable in the real world. Although the COURAGE trial excluded 10,000 patients without reference to coronary anatomy (5,100 without ischemia and 4,900 with an inadequate ejection fraction) (3), they stipulate that “coronary angiography...should not be denied to patients with stable angina pectoris,” because the “choice of therapy(s) for each individual patient must be made based on coronary anatomic suitability” (2).
Counterpoint. The contention that most patients already receive medical therapy is highly suspect. While the actual numbers are open to debate, the simple fact is that many patients with stable angina (and an additional number of asymptomatic patients) are undergoing PCI without having received sufficient medical therapy. On the conservative assumption that 1 million procedures are being performed each year, at least 30% of them in stable patients who could otherwise be treated medically (2), that is 300,000 procedures that might be deferred. Even if one-third of them eventually cross over to revascularization, that is still 200,000 fewer procedures—at a saving of at least $6 billion annually at current levels of reimbursement. Formal assessments of cost-effectiveness and quality of life are unlikely to contravene these projections (35).

Nevertheless, the suboptimal quality of medical therapy outside of the COURAGE trial remains a problem. Many patients are not treated at all, and those who are do not adhere to treatment for very long (36). But, the recommendation of unconditional coronary angiography is no solution and might encourage unnecessary revascularizations. Bad behavior by some cannot justify equally bad behavior by others. The preferable solution would be better medical treatment rather than more intervention.

The COURAGE trial itself provides the best justification for improving the quality of medical therapy, and payers are beginning to take note. Aetna (among others) is now offering proven preventive medications such as those in the COURAGE trial free of charge to patients with known heart disease or diabetes (37). It is trials such as the COURAGE trial that encourage such innovations.

Implications

In the end, the inference in the COURAGE trial is not that OMT is better than PCI, but that an initial recommendation of PCI+OMT offers no important advantage over an initial recommendation of OMT alone (38). Percutaneous coronary intervention can be reserved for a later time with little risk that an unfavorable event will intervene. As was true in the CASS (Coronary Artery Surgery Study), a wait-and-see strategy is justified.

Why will so many of us resist this rational and prudent conclusion (13)? Some will point to the personal, professional, and political capital that is at stake, but there are deeper reasons. In his landmark sociologic dissection of the medical profession, Eliot Freidson identifies 5 traits that characterize the typical clinician (39):

We believe in what we are doing. When things go right, we take the credit.
We prefer action to inaction. Even action with little chance of success is preferred over no action at all. We are pragmatic. We see apparent cause-effect relationships even in the absence of any theoretic foundation. We are highly subjective. We depend more on “gut feelings” than on “book knowledge.”

We emphasize uncertainty in our defense. When things go wrong, it is not our fault. Because we deal with individuals rather than groups, we cannot rely on epidemiologic concepts or probabilities derived from population statistics.

Although these traits usually serve us well, they invite intellectual gerrymandering. Thus, when the evidence conflicts with our judgment we tend to resist it, but when the evidence is consistent with our judgment we tend to embrace it. As a result, if there is even a 1% chance that some technologic advance is marginally better than the status quo (think tissue plasminogen activator versus streptokinase or bivalirudin versus heparin), we act as if it is a certainty and discount the downside.

The Centers for Disease Control, however, report that coronary heart disease deaths in the U.S. fell not 1% but more than 40% from 1980 to 2000 (40). Nearly one-half of coronary heart disease deaths in the U.S. fell not 1% but >80% years) (from the New York State Angioplasty Registry). If we are pragmatic, we see apparent cause-effect relationships even in the absence of any theoretic foundation. We are highly subjective. We depend more on “gut feelings” than on “book knowledge.”

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The Centers for Disease Control, however, report that coronary heart disease deaths in the U.S. fell not 1% but more than 40% from 1980 to 2000 (40). Nearly one-half of this drop was attributable to treatment of conventional risk factors and only 7% to revascularization. According to the study’s senior author, “There has been a huge amount of money spent on angioplasty and [bypass surgery], with the prevailing understanding that it prevents deaths, but this is the flashy stuff and it doesn’t make a great deal of difference” (41).

It takes COURAGE to say that.

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REFERENCES