POINT

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INTERPRETING THE COURAGE TRIAL

It takes COURAGE to alter our belief system

To a man with a hammer, a lot of things look like nails that need pounding.
—Attributed to Mark Twain

THE CLINICAL OUTCOMES UTILIZING REVASCULARIZATION AND AGGRESSIVE DRUG EVALUATION (COURAGE) trial,[1] in which I was the co-principal investigator, was designed to determine whether percutaneous coronary intervention (PCI) coupled with optimal medical therapy reduces the risk of death or nonfatal myocardial infarction (MI) in patients with stable coronary artery disease, as compared with optimal medical therapy alone. Such a "strategy trial" had never been conducted since the advent of angioplasty in 1977.

See the accompanying introduction by Dr. Deepak Bhatt on page 618 and the "counterpoint" article by Dr. Dean Kereiakes on page 637.

We found that, *as an initial management strategy in patients with stable coronary artery disease*, PCI did not reduce the incidence of death, MI, or other major cardiovascular events when added to optimal medical therapy.

Not surprisingly, these results have prompted intense introspection, dialogue, discourse, and controversy since their publication in March 2007. Why has COURAGE become such a lightning rod for believers and skeptics?

*Dr. Boden has disclosed that he has received consulting fees or honoraria from Abbott Laboratories, Bristol-Myers Squibb, CV Therapeutics, Merck, PDL BioPharma, and Pfizer.

DOES COURAGE TELL US ANYTHING NEW?

Some state that COURAGE tells us little that is novel or surprising. Not so. This trial has added important scientific information on a topic on which little had been published: the role of PCI in reducing long-term "hard" clinical events (ie, death or MI) in patients with chronic stable angina —a group that includes millions of patients worldwide.

Before COURAGE, the randomized, controlled trials (N = 11) that prospectively addressed the benefit of PCI vs medical therapy included fewer than 3,000 patients, most of them at low risk.[2] Excluding the second Randomised Intervention Treatment of Angina (RITA-II) trial,[3] with 1,018 patients, the remaining 10 randomized controlled trials involved fewer than 1,950 patients.[4–13]

Given this paucity of prospective data, it is scientifically unsound to assert that COURAGE merely tells us what we already know, particularly considering that tens of millions of patients worldwide with stable coronary artery disease have undergone PCI electively for chronic angina over the past 30 years. Because PCI in such patients has become so commonplace, and because the data in support of a durable clinical benefit beyond mere angina relief are so sparse, undertaking the COURAGE trial to address the important issue of prognostic benefit is of immense scientific importance.

In reality, the COURAGE results are not that surprising—but not for the reasons many cite.

COURAGE has added important scientific information on the role of PCI vs optimal medical therapy in stable angina

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PCI PROVEN BENEFICIAL IN MI, BUT NOT IN STABLE CORONARY ARTERY DISEASE

Advances 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 MI clearly indicate that non-flow-limiting coronary stenoses are the principal progenitors of most "hard" clinical events.[14–16] We now know that coronary occlusion following plaque rupture or fissuring is an emergency that cannot be optimally managed pharmacologically. Abundant data from clinical trials show that urgent or emergent PCI in patients with ST-segment-elevation MI or high-risk non-ST-segment-elevation MI reduces the rates of death or subsequent MI.[17–22] The COURAGE trial does *not* challenge this fact.

However, performing elective PCI in patients with chronic angina and stable coronary artery disease is virtually identical procedurally to that performed in patients with acute coronary syndromes. Thus, many have accepted the broader premise that PCI would confer a more durable clinical benefit (ie, beyond angina relief or improved exercise performance) in patients with chronic angina and stable coronary artery disease as well. This belief system is rooted in a scientifically plausible clinical construct that dilating one or more flow-limiting coronary stenoses would be inherently superior to an approach that involved only pharmacologic and lifestyle interventions, but this premise was unproven. Thus, the hypothesis that we tested in COURAGE—that PCI, coupled with optimal medical therapy, would be superior to optimal medical therapy alone.

Non-flow-limiting coronary stenoses are the progenitors of most hard clinical events

THE RATIONALE FOR THE COURAGE DESIGN

In interpreting the results of the COURAGE trial, we must understand the historical context in which it was designed.

COURAGE was initially conceived in 1996, when intracoronary stenting was still in its infancy, and only one PCI trial,[4] comparing balloon angioplasty vs medical therapy in 212 patients with single-vessel coronary artery disease, had been published.

Other relatively small trials followed, but only RITA-II[3] compared the long-term outcomes (mean 2.7 years) of PCI (balloon angioplasty) and medical therapy, with death or MI as the primary outcome measure. Although the outcomes were worse with angioplasty, most physicians felt that the results were not clinically meaningful, given that PCI continued to evolve and stents came into widespread use.

Of note, in all the randomized clinical trials before COURAGE, medical therapy was configured in apposition to PCI, not as part of a comprehensive, additive systemic-plus-focal management strategy. COURAGE was uniquely designed with a goal of advancing a novel and contemporary treatment paradigm that PCI *coupled with* optimal medical therapy would be superior to optimal medical therapy alone in reducing a composite clinical end point of death or MI in patients with chronic stable angina undergoing largely elective PCI.

Why superior? Several prominent interventional cardiologists in the United States helped plan the COURAGE trial, and they were unanimous that a superiority design was the most scientifically appealing and in keeping with prevailing clinical practice philosophy. They concurred that an "equivalence design" would be inherently weaker and viewed with skepticism by the interventional community, who might interpret such a design as subterfuge for a hidden agenda to undermine PCI. Thus, both academic and practicing cardiologists were united in the belief that such a superiority design trial was most worthy of prospective scientific study.

STRENGTHS AND LIMITATIONS OF THE COURAGE TRIAL

What are the strengths and limitations of the COURAGE trial, and what have been the principal reasons for disagreement in interpreting the results? I will attempt to address these issues and concerns systematically.

Both groups received optimal medical therapy

Unlike earlier studies that used only modest anti-ischemic therapy as the comparator or, as in the Atorvastatin Versus Revascularization

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Treatment (AVERT) trial,[5] used high-dose statin therapy only in the medical therapy group but not in the PCI-treated patients, COURAGE used aggressive therapy with drugs (aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, statins) that had been proven to be of clinical benefit in individual randomized, placebo-controlled trials. Importantly, in COURAGE, these agents were used together in both the PCI group and the optimal medical therapy group so as not to deprive the PCI group of the known benefits of intensive secondary prevention.

No other trial had ever attempted such comprehensive treatment in coronary patients, nor had any trial ever attempted to incorporate guideline-driven best practices to achieve and maintain multiple treatment targets during long-term follow-up.

COURAGE assessed 'hard' end points

We chose the primary outcome measure of death or MI, with long-term follow-up, since such a composite end point was also the benchmark used in the earlier trials of coronary artery bypass graft surgery vs medical therapy in the 1970s and 1980s.[23,24] Most clinical decisions about adopting various treatments in medical practice are predicated on demonstrating efficacy in such robust end points, and the decision to use a "hard" clinical outcome composite was in keeping with historical standards of trial design.

MI was rigorously defined

Another strength of the trial (frequently misperceived by its critics) is how MI was defined.

Contrary to statements that there was a single biomarker definition for MI and that any periprocedural elevation of the creatine kinase-MB fraction (CK-MB) qualified as an MI and therefore counted in the primary outcome, we defined MI in three ways:

- **Spontaneous MI** required a CK-MB level of at least 1.5 times the upper limit of normal or a troponin level of at least 2.0 times the upper limit of normal.
- **Peri-PCI MI** required an CK-MB value of at least 3.0 times the upper limit of normal or a troponin value at least 5.0 times the upper limit of normal.
- **Perioperative MI** (after coronary artery bypass grafting) required an MB-CK or troponin elevation of at least 10.0 times the upper limit of normal.

All cases of suspected MI required signs and symptoms of an acute ischemic syndrome along with the above abnormal biomarkers to qualify as a "COURAGE MI."[1]

Even when we excluded periprocedural MI from the primary end point, there was no significant difference in outcomes between the PCI and optimal medical therapy groups.[1]

A limitation: Population was not as diverse as hoped

COURAGE was a large trial and was carried out in US Department of Veterans Affairs (VA) hospitals, non-VA US hospitals, and Canadian hospitals. We wanted the patient population to be heterogenous in terms of geographic location, ethnicity, clinical characteristics, and health care systems, so as to be broadly representative of clinical practice.

We expected that one-third of patients would be from VA sites, one-third from non-VA US sites, and one-third from Canadian sites. However, ultimately only 17% of COURAGE patients were from non-VA US sites, presumably because of: a) a deep-seated belief that favored the presumed superiority of PCI in such patients who were trial-eligible; b) pressure from referring or treating physicians that failure to provide PCI to patients with symptomatic coronary heart disease constituted inferior management; or c) medical-legal concerns surrounding the risk for potential litigation in not performing PCI on patients with flow-limiting stenoses.

This pattern of recruitment, together with low numbers of women (15%) and nonwhite patients (14%), was the most significant trial limitation.

The primary end point in COURAGE: death or MI during long-term follow-up

Quality of life measured

A particularly important design feature and strength of COURAGE was that prospective health status assessment using the Seattle Angina Questionnaire (SAQ) and Short Form-36 instruments was imbedded in the trial proper and represents the most comprehensive approach to quantifying patient-centered outcomes ever undertaken in a large

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strategy trial of coronary heart disease management. These quality-of-life data will permit unique and unparalleled opportunities to correlate patient-centered outcomes (eg, symptoms, physical functioning, and other health status domains) with clinical outcomes during long-term follow-up. Additionally, detailed measures of cost-effectiveness and resource utilization will permit rigorous and comprehensive prospective assessment of the health economic implications of the PCI plus optimal medical therapy vs optimal medical therapy management strategies in a manner never before attempted or undertaken in a large-scale clinical trial.

New therapies adopted during trial

By design, we decided to adopt therapeutic advances that would become accepted into clinical practice (or that would result in modifications in the American College of Cardiology/American Heart Association treatment guidelines) during the trial. Examples:

- New drugs that were approved after COURAGE was launched in mid-1999, such as ezetimibe (Zetia) and extended-release niacin
- New uses for existing drugs, such as clopidogrel (Plavix) for acute coronary syndromes and for standard post-PCI treatment for up to 12 months
- More aggressive management of low-density lipoprotein cholesterol (LDL-C), with an optional target of less than 70 mg/dL in patients at high risk.

Even before the major lipid trials that altered clinical practice were published,[24–26] the COURAGE protocol called for an aggressive LDL-C target of 60 to 85 mg/dL. Secondary lipid targets were a high-density lipoprotein cholesterol value greater than 40 mg/dL and triglycerides less than 150 mg/dL.

Undoubtedly, these design features contributed to the clinical benefits achieved with optimal medical therapy.

Would drug-eluting stents have changed the outcomes?

Drug-eluting stents were not approved by the US Food and Drug Administration until about 6 months before the end of enrollment, and their manufacturers repeatedly denied our efforts to acquire them for use in COURAGE.

If we had been able to use more drug-eluting stents, the angina-free outcomes in the PCI group might have been even better, and the incidence of repeat revascularization (21% during a median of 4.6 years) might have been even lower. On the other hand, several randomized trials[27–32] found no evidence that drug-eluting stents are superior to bare metal stents in reducing the rates of death or MI. In fact, in a large Swedish registry,[32] the mortality rate was significantly higher with drug-eluting stents.

Accordingly, there is little reason to suspect that drug-eluting stents would have altered the primary outcome in COURAGE.

Did COURAGE have enough statistical power?

COURAGE has been criticized as being "underpowered" for the primary outcome measure of death (from any cause) or MI.

When COURAGE was designed, few studies could be used for statistical modeling to predict event rates. Because we designed COURAGE to include mostly patients with symptoms of persistent angina (88% had angina at baseline), and further required objective findings of myocardial ischemia at baseline with either new resting ST-segment shifts or objective evidence of inducible ischemia (95% met these criteria), *and,* of importance, required that there be 70% or greater stenosis of a major epicardial coronary artery by visual assessment in all patients, we reasoned that these rigorous inclusion criteria defined a pool of patients at moderate to high risk with chronic angina and stable coronary artery disease, and we estimated the event rates accordingly.[33]

All patients in COURAGE were treated aggressively to multiple medical targets

Additionally, when the American College of Cardiology and the European Society of Cardiology revised their definition of MI in 2000 and established troponin elevations as the new gold standard for myocardial necrosis, the COURAGE Executive Committee and Data Safety Monitoring Board recommended that troponin-positive acute coronary syndromes be included as part of the primary outcome measure in the trial. This, combined

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with a decision to extend enrollment by 18 months and follow-up by 6 months, resulted in a revised sample size of 2,270 as the minimum required to address the above hypothesis with 85% power.[33]

While the overall number of primary events during a median of 4.6 years of follow-up was lower than projected, other recent large trials have also had lower-than-projected event rates,[34,35] and are likely a reflection of the clinical benefits associated with intensive medical therapy used in contemporary trials.

Speculative post hoc power calculations are largely inappropriate and counterproductive, particularly since the Kaplan-Meier life-table curves for the primary outcome measure of death or MI were virtually superimposable for the two randomized groups over the initial 4.5 years of follow-up (hazard ratio 1.05, 95% confidence interval [CI] 0.87–1.27), meaning that there is a 95% chance that the true benefit/harm (of which the point estimate reported lies in the middle) is within the range cited. Viewed from the opposite perspective, the 95% CI excludes a potential benefit of PCI of greater than 13%—ie, there is 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).[1] This means it is exceedingly unlikely that we missed a true PCI benefit.

None of the 8 prespecified subgroups showed any significant benefit from PCI

COURAGE PATIENTS WERE AT MODERATE TO HIGH RISK

Some have stated that the COURAGE patients were at low risk and that the event rates were low over the course of follow-up. However, little evidence supports either contention.

At baseline, 34% of the COURAGE patients had diabetes, 71% had dyslipidemia, 67% had hypertension, 29% were current smokers, 39% had prior MI, and 26% had undergone previous revascularization.[36] Their mean body mass index was 30 kg/M^2, and approximately 60% met the current definition of metabolic syndrome. Most (58%) were in Canadian Cardiology Society anginal class II or III, and 30% were in class I (12% had asymptomatic myocardial ischemia).

The mean number of anginal episodes per week was 6, while the median was 3. (We originally reported[36] that the mean number of anginal episodes per week was 10, but this value was incorrect, and an erratum is in press in the *American Journal of Cardiology*.) Thus, there is no evidence that there were two distinct patient subpopulations in COURAGE, or that there was a higher crossover rate in a more symptomatic subset of the overall study group.

A total of 95% of patients underwent ischemia testing, and of those who underwent myocardial perfusion scintigraphy, two-thirds had multiple reversible perfusion defects and the remaining one-third had a single reversible perfusion defect. Almost 70% of patients had multivessel coronary artery disease (≥ 70% diameter stenosis estimated visually). Left anterior descending coronary disease was common, being present in 37% in the medical therapy group and 31% in the PCI group (a difference that was statistically significant).

Together, these findings signify that the patients had considerable symptoms at baseline, appreciable clinical comorbidity, a high prevalence of objective evidence of myocardial ischemia, and extensive angiographic coronary artery disease.[1,36] These are the very features that would characterize the type of patient (at moderate to high risk) who would be expected to benefit from PCI.

The rate of death or MI at a median 4.6 years of follow-up was approximately 19% in both groups (4.13% per year), and the rate of death, MI, or stroke was approximately 20% (4.35% per year). These rates clearly show that COURAGE patients were at moderate to high risk, not low risk.

SUBGROUP ANALYSES CAN GO TOO FAR

The outcomes of PCI in COURAGE (especially in the VA and Canadian hospitals) have been repeatedly portrayed as being discordant with and of lower quality than contemporary US clinical practice.

However, none of the eight prespecified subgroups showed any significant benefit from PCI, and the interaction *P* value for all comparisons was likewise nonsignificant across health care sectors. While point estimates for

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the primary end point appear to favor PCI in women (n = 338) and non-VA US patients (n = 387), the 99% CIs for both comparisons breach the unity boundary and thus are not statistically significant. Attempts to perform post hoc chi-square assessments in these two subgroups on the basis of the point estimates alone is statistically inappropriate and, because these two subsets have the smallest number of patients among the predefined covariates, efforts to overinterpret such very small subgroups are inherently unstable and statistically unreliable.

The angiographic outcomes of PCI in COURAGE compare favorably with those of previously published stent trials.[27–32] Although some suggest that outcomes of PCI were worse in the VA and Canadian sites, no data support this claim. Rates of angiographic success were nearly identical across health care systems, as was the acuteness of disease. Furthermore, at baseline, the patients at the non-VA US sites had lower rates of diabetes, hypertension, smoking, prior MI, and prior revascularization than VA patients,[36] and thus were at lower risk overall. Because the subset of non-VA US patients was so small, perceived differences in clinical outcomes between the PCI and optimal medical therapy groups may reflect merely the play of chance or a type II error. [1]

'INCOMPLETE REVASCULARIZATION' MISSES THE POINT

Among the 94% of COURAGE PCI patients who received stents, 59% received one stent and 41% received two or more stents. Because 69% of the patients had significant multivessel coronary artery disease 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 of why PCI was not beneficial.

COURAGE tested a strategy of routine, anatomically driven PCI plus optimal medical therapy vs a strategy of selective, ischemia-driven PCI if initial optimal medical therapy failed. As such, COURAGE was not designed or undertaken to compare "complete" vs "incomplete" revascularization, as the investigators and operators were encouraged to perform PCI on the culprit lesion or lesions that were deemed to be causing the chronic coronary syndrome. While a core angiographic laboratory did subsequently assess angiographic and operator success using quantitative coronary angiography (another strength of the trial), all decisions regarding PCI usage in the trial were clinically directed by the site investigator/operator using standard visual angiographic assessments.

A preliminary analysis from the Coronary Angiography Core Laboratory (personal communication: G.B. John Mancini, MD) has been undertaken to address this concern and, excluding the subset of patients with chronic total occlusion in whom PCI was not attempted (presumably for sound clinical reasons, such as vessels that were chronically totally occluded subtending nonviable myocardial segments, or absent regional wall motion), approximately 84% of COURAGE patients with a coronary stenosis of 70% or greater (determined by quantitative coronary angiography) achieved complete revascularization (one-, two-, or three-vessel disease before PCI converted to "0-vessel disease"), and 8% achieved "partial revascularization" (two- or three-vessel disease converted to one- or two-vessel disease), indicating an overall high rate of successful revascularization of stenotic coronary arteries that were amenable to PCI.

There were also no differences in success rates across health care systems. There is no evidence that the quality of PCI as performed in COURAGE, or the achievement of high levels of revascularization in the majority of patients with multivessel coronary artery disease, fell below the accepted standard achieved in real-world contemporary clinical practice.

COURAGE does *not* tell us to delay or defer primary PCI for ST-segment-elevation MI or for high-risk acute coronary syndromes

IMPORTANCE OF ACHIEVING MEDICAL TREATMENT TARGETS

The achievement in COURAGE that is perhaps the most important and least controversial is the impact that intensive medical therapy and lifestyle intervention had on mitigating clinical events in both treatment

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groups during long-term follow-up. While many have attempted to portray COURAGE as a battle between management strategies in stable coronary patients with chronic angina, the most pivotal take-home message is that *optimal medical therapy as an initial management strategy in such patients is both safe and effective*.

The COURAGE results do not indicate that PCI is ineffective or inappropriate as an initial management strategy in stable coronary disease; they show that PCI is not the only viable and clinically defendable initial strategy and that optimal medical therapy alone may be suitable and appropriate for many patients (and physicians) who may decide to defer PCI until after an assessment of the efficacy of optimal medical therapy can first be made.

Of importance: COURAGE does not tell us to delay or defer primary PCI for ST-segment-elevation MI or for high-risk acute coronary syndromes.

COURAGE does indicate that optimal medical therapy has evolved at a level commensurate with catheter-based revascularization over the last decade and that risk reduction and optimal medical therapy need to be central tenets of optimal patient management to prevent subsequent plaque rupture and its consequences (ie, death, MI, or hospitalization for acute coronary syndromes) in patients with stable coronary artery disease, regardless of the decision to undertake or defer PCI.

Coronary disease is a fundamentally systemic problem that requires systemic treatment

While the optimal medical therapy in COURAGE, with its remarkable benefits, has been almost universally praised, some have tried to downplay the results as being too difficult to achieve in the real world of clinical practice. On the contrary, we should make optimal medical therapy a goal for the millions of patients worldwide who can reap the sustained benefits of clinical event reduction.

Recently, Kaul et al,[37] in a provocative position paper on the future directions of stenting, advocated several evidence-based proposals, including a renewed emphasis on medical therapies with proven long-term benefit, kinetic modeling to estimate long-term outcomes of therapies based on the available near-term data, and restructuring of reimbursement incentives to encourage wider use of evidence-based clinical management strategies.

IMPLICATIONS FOR CLINICAL PRACTICE

Coronary artery disease is fundamentally 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 acute coronary syndromes. Optimal medical therapy is directed toward stabilizing so-called vulnerable plaques that are frequently mild angiographically and nonobstructive.

Therefore, optimal medical therapy should be the preferred therapeutic approach to reducing clinical events in patients with chronic coronary syndromes, used in a complementary manner with focal revascularization approaches directed toward angina and ischemia relief, if needed. Achieving and maintaining multiple treatment targets may be difficult, but are well worth the effort.

Whether COURAGE will change clinical practice in the United States presently remains unclear. While no one trial is likely to result in profound change, there is reason to believe that COURAGE will re-orient our clinical thinking away from what has been a largely procedural approach to initial patient management for stable coronary artery disease. Medicine in general, and cardiology in particular, is a rapidly evolving discipline in which art and science frequently converge.

COURAGE confronts conventional wisdom and an existing belief system that chronic angina, objective evidence of ischemia, and significant obstructive coronary artery disease may not inevitably require myocardial revascularization as an initial management strategy. The results are consonant with current clinical practice guidelines that optimal medical therapy should be considered an appropriate and favored first approach in stable coronary artery disease.[38] COURAGE may well alter the belief systems of many physicians who will synthesize the trial results and seek to achieve equipoise in their clinical decision-making between PCI plus optimal medical therapy vs optimal medical therapy alone. ■

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