

The Truth and Consequences of the COURAGE Trial

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Percutaneous coronary intervention (PCI) has played an integral role in the therapeutic management strategies for patients who present with either acute coronary syndromes or stable angina pectoris. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial enrolled patients with chronic stable angina and at least 1 significant ($\geq 70\%$) angiographic coronary stenosis who were randomly assigned to an initial treatment of either PCI in conjunction with optimal medical therapy or optimal medical therapy alone. Although the initial management strategy of PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events, improvement in angina-free status and a reduction in the requirement for subsequent revascularization was observed. An in-depth analysis of the COURAGE trial design and execution is provided. (J Am Coll Cardiol 2007;50:1598–603) © 2007 by the American College of Cardiology Foundation

Since the introduction of coronary balloon angioplasty by Gruentzig in 1977, significant evolution has occurred in both catheter-based percutaneous coronary intervention (PCI) as well as adjunctive pharmacotherapies. Since balloon angioplasty was supplanted by bare-metal stents (BMS), and subsequently drug-eluting stents (DES), a series of randomized comparative clinical trials have demonstrated a progressive decline in both angiographic and clinical restenosis with each technologic iteration. However, no discernible differences in the occurrence of death or recurrent myocardial infarction (MI) have been observed during device evolution (1–3). Similar iterative improvements in medical therapy for symptomatic coronary artery disease (e.g., lipid-lowering, antiplatelet, blood pressure, and diabetic therapies) have been associated with improved clinical outcomes. Although both aggressive and preemptive

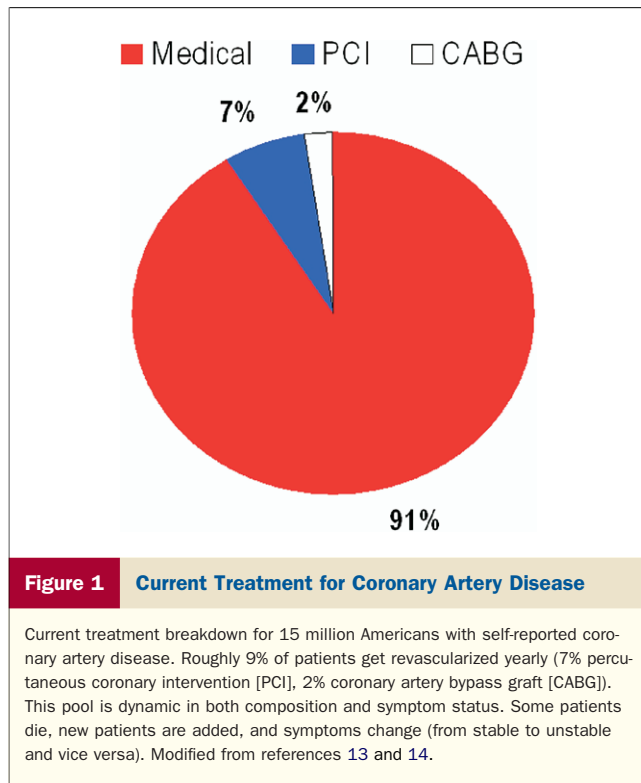
use of PCI for ST-segment elevation MI as well as early angiography and PCI for non-ST-segment elevation acute coronary syndromes have been demonstrated to improve survival and to reduce the incidence of death or nonfatal MI compared with aggressive medical (nonrevascularization) therapy alone (4–6), the prescription for performing PCI in patients with stable symptomatic coronary stenoses has remained limited to the relief of symptoms and improvement in quality of life (7–11).

Not surprisingly (and in concert with multiple prior studies comparing PCI to medical therapy in stable angina patients), the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial reaffirms the premise that an initial management strategy of PCI using BMS does not reduce the risk of death, MI, or other major cardiovascular events when added to “optimal” medical therapy compared with optimal medical therapy alone (12). Because this observation appears to be neither novel nor surprising, why has it generated so much public and professional interest? To understand what (if any) implications this trial should have for current clinical practice (the “consequences”), let us first closely examine the construct, execution, and observations of the COURAGE trial (the “truth”).

Because atherosclerotic cardiovascular disease remains the major cause of death and/or disability in the industrialized world, iterative developments in treatment strategies may

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have broad public health policy implications. Currently, at least 15 million Americans self-report the presence of coronary artery disease, with ~2 million diagnostic catheterizations, ~1 million PCIs (~60% for unstable angina, 10% for acute MI, and 30% for stable angina), and ~350,000 coronary artery bypass operations performed yearly (Fig. 1) (13,14). Thus, because approximately 9% get revascularized each year (7% PCI, 2% surgery), the vast majority of Americans receive medical therapy for their coronary artery disease. Before attempting to extrapolate the results of the COURAGE trial to the broader scope of clinical practice, we must first examine the study population and the treatment(s) prescribed.

Almost 36,000 patients were screened for the COURAGE trial, from which 3,071 (8.6%) met eligibility criteria and 2,287 (6.3%) were subsequently randomized. Of the 1,149 patients randomly assigned to PCI, 73 either did not have the procedure or had a stenosis that “could not be dilated” and 107 were lost to follow-up. Thus, 15.7% of patients assigned to PCI were either not treated or did not complete follow-up. Conversely, 97 (8.5%) of the 1,138 patients assigned to medical therapy (no initial PCI) were lost to follow-up. Importantly, although all patients had at least 1 coronary vessel with a proximal $\geq 70\%$ angiographic stenosis (almost 70% had ≥ 2 -vessel disease with at least 1 vessel suitable for PCI) associated with objective evidence of myocardial ischemia, nearly 80% had minimal or no angina (Canadian Cardiovascular Society [CCS] class II or less with a median duration of 5 months), and left ventricular ejection fraction was well preserved (mean ~61%). The trial design prospectively specified that no more than 10% of

medically treated patients would cross over to PCI in the first 4 years to manage patients who developed severe or progressive angina during follow-up (15).

High levels of compliance with medical therapies were observed throughout the COURAGE trial, and at 1, 3, and 5 years of follow-up in the medically treated cohort compliance rates were 95%, 95%, and 94% for aspirin, 95%, 92%, and 93% for statins, and 89%, 86%, and 86% for beta-blockers, respectively. Approximately 70% of patients achieved a low-density lipoprotein level < 85 mg/dl, 65% and 94% of patients achieved systolic and diastolic blood pressure targets of < 130 and < 85 mm Hg, respectively, and 45% of diabetic patients achieved a hemoglobin A_{1c} level of $\leq 7.0\%$. Thus, both compliance with multiple evidence-based medical therapies and achievement of treatment targets were exemplary in this trial.

In this context, several important questions arise. First, and foremost, are these findings new? Multiple studies and meta-analyses have previously demonstrated that revascularization by either PCI (6–11,16) or coronary bypass surgery (17–22) does not improve the already excellent survival of stable angina patients on optimal medical therapy (Table 1). This lack of demonstrable benefit for reduction in death or nonfatal MI stands in contrast to the clear benefit observed following PCI (vs. medical therapy) in both ST-segment elevation and non-ST-segment elevation acute coronary syndromes (4–6). Therefore, the “failure” of PCI in the COURAGE trial to meet the hypothesized aggressive end point of a 22% reduction in death or nonfatal MI compared with medical therapy alone in stable angina patients is neither surprising nor new. Indeed, given the weight of earlier randomized controlled clinical trial evidence, a noninferiority trial design may have been more appropriate.

Importantly, the power analysis assumptions made by the COURAGE trial must be closely examined. A total of 3,260 patients initially were to have been enrolled to accrue a prespecified 614 primary end point events based on a projected 3-year rate of death or MI of 21% in patients assigned to medical therapy alone. During the course of the study, the definition of MI was changed to include patients with an elevated troponin and the durations for both randomization and follow-up were extended. Despite the liberalized definition of MI and extended duration of follow-up, the observed rate of death or MI in medically treated patients to 3 years of follow-up was only 12% (413 end point events, or 67% of the projected requirement), so that the trial remains underpowered. Because patients were enrolled after coronary angiography, those with severe and/or complex stenosis may not have been included, and investigator bias in patient selection toward lower angio-

Abbreviations and Acronyms

- BMS** = bare-metal stent(s)
- CCS** = Canadian Cardiovascular Society
- DES** = drug-eluting stent(s)
- MI** = myocardial infarction
- PCI** = percutaneous coronary intervention

Table 1 Summaries of Trials Comparing Medical Therapy Versus PCI for Stable Coronary Artery Disease Patients

Trial (Ref. #)	Mortality and MI	Angina Relief	QOL	Repeat Revascularization
RITA-2 (7)	No difference	PCI	PCI	PCI
ACME (8)	No difference	PCI	PCI	PCI
ACME-2 (16)	No difference	PCI	PCI	NA
MASS (9)	No difference	PCI	NA	No difference
MASS-II (11)	No difference	PCI	PCI	No difference
AVERT (10)	No difference	PCI	PCI	No difference
TIME*	No difference	PCI	PCI	PCI
COURAGE (12)	No difference	No difference	PCI	PCI

*TIME Investigators. *Lancet* 2001;358:951–7.

MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; QOL = quality of life.

graphic risk cannot be excluded. This premise (lower-risk patients enrolled) would appear to be supported by the relatively low (0.4%) annual cardiac mortality observed in the entire study cohort. Furthermore, the use of all cause death in the primary end point may have obscured the ability to differentiate between treatment strategies, because PCI would not be expected to reduce noncardiac-related death compared with medical therapy. Of note, only 48 deaths (26.7% of total) were confirmed to be cardiac related in this trial. Finally, the COURAGE trial used the definition of symptoms accompanied by any creatine kinase-MB enzyme elevation above normal to define periprocedural (PCI) MI (15). Such a broadly inclusive definition enhanced end point accrual but, no doubt, disadvantaged PCI and has little, if any, real prognostic import (23,24).

Second, was the performance of PCI optimal in this trial? Unfortunately, the absence of a formal angiographic core laboratory analysis in the COURAGE trial makes accurate assessment of stenosis location and severity as well as determination of angiographic procedural success rates more difficult. In this context, operator-assessed per-lesion success rates were only 93% and did not take into account those patients in whom the stenosis could not be crossed or those in whom PCI was not attempted. Considering the trial design and execution, it is perhaps surprising that PCI did as well as was observed for reducing angina symptoms (versus medical therapy alone) during the first 3 years of study follow-up. Despite the fact that ~70% of patients assigned to PCI had ≥ 2 -vessel disease, only 36% received >1 stent and only 2.7% were treated with a DES. Indeed, partial and/or incomplete revascularization of patients with multivessel disease has repeatedly been associated with worsened clinical outcomes (vs. complete revascularization) (25–27), particularly with an increase in the requirement for repeat revascularization procedures. This fact may at least in part explain the observation that 21.1% of PCI-treated patients in the COURAGE trial required an additional revascularization procedure at a median of 10 months of follow-up. We are not informed how many of these additional procedures were performed for BMS restenosis, remaining untreated stenoses, or progression of disease that was initially considered noncritical. These observations are

similar to those from a recent analysis of the New York State Angioplasty Database, where incomplete revascularization was associated with more frequent additional revascularization procedures in follow-up as well as a relative (25% to 35%) increase in mortality (25).

In addition, disparity in outcomes after PCI was observed based on where the procedure was performed. For example, those patients treated outside of the U.S. Veterans Administration (VA) hospital system demonstrated a 29% relative reduction in the primary end point (death or MI) after PCI compared with medical treatment alone (15% vs. 21%, respectively). Although too few patients were enrolled outside of the VA system to provide adequate statistical power for analysis, this magnitude of primary end point reduction would satisfy the primary hypothesis of the trial. In addition, apparent differences in the composite occurrence of death or MI between U.S. (~21% to 22%) and Canadian (~14%) patients are not explained.

The use of revascularization in the medically treated cohort significantly clouds interpretation of a 72% “angina-free” status for this subgroup at 5 years, given that 43% of these patients began the trial with minimal (CCS class I) or no angina and 32% were subsequently revascularized for severe or worsening symptoms (and were counted in the medically treated cohort by intention to treat). In this context of randomized controlled trials comparing medical therapy with PCI in stable coronary disease patients (7–11), only the COURAGE trial failed to observe a relative benefit of PCI for providing long-term angina relief (Table 1) (12). One potential explanation for this observation is that patients enrolled in the COURAGE trial experienced at baseline a mean of 10 and a median of 3 anginal episodes weekly as reported in 3 separate publications (12,15,28). This skewed distribution suggests the presence of 2 patient populations and may have contributed to the higher-than-predicted crossover rate (32%) to PCI in the more symptomatic subpopulation. Of note, an “erratum” revising the mean angina frequency to 6 episodes weekly is apparently pending publication (29).

Only 2.7% of the COURAGE trial PCI patients were treated with a DES. The relative benefit of DES compared with BMS for reducing clinically driven repeat revascular-

ization (50% to 70% relative reduction) has been repeatedly demonstrated in randomized controlled clinical trials (30–32). The DES (compared with BMS) has provided a marked reduction in both clinical as well as angiographic (70% to 80% relative reduction) restenosis, with no significant differences observed in the occurrences of death or nonfatal MI (3,30–32). Freedom from clinically driven repeat revascularization is a surrogate for freedom from angina, improved exercise tolerance, and enhanced quality of life. Therefore, one could reasonably predict that a strategy of complete revascularization by PCI using DES in the COURAGE trial would have reduced the need for repeat revascularization procedures and would have improved the angina-free symptom status of the PCI cohort. Indeed, repeat revascularization rates to 1 year of follow-up have been comparable in comparisons of coronary artery bypass surgery with multivessel PCI using DES from both the ERACI (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Artery Bypass Surgery in Patients With Multiple-Vessel Disease)-II/III and the ARTS-II (Arterial Revascularization Therapies Study Part II: Sirolimus-Eluting Stents for the Treatment of Patients With Multivessel de Novo Coronary Artery Lesions) trials (33–35). These observations suggest that comparable clinical benefit (reduction in angina and revascularization) may be provided by complete PCI using DES and coronary bypass surgery in patients with multivessel disease but await more definitive confirmation by ongoing randomized controlled clinical trials such as the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) (36), FREEDOM (Comparison of Two Treatment for Multivessel Coronary Artery Disease in Individuals With Diabetes) (37), CARDIA (Coronary Artery Revascularization in Diabetes) (38), and VA CARDS (Coronary Artery Revascularization in Diabetes) (39) trials. Nevertheless, despite the limitations of PCI as used in the COURAGE trial, there remained a significant reduction in the requirement for revascularization at follow-up to a median of 4.6 years (21.1% vs. 32.6%; $p < 0.001$), as well as improvement in quality of life accompanied by a reduction in perceived physical limitation and angina frequency in those patients initially assigned to PCI compared with medical therapy alone (12,40). In this context, a 13% relative reduction in mortality to 4.6 years of follow-up was observed after an initial PCI strategy.

Finally, are the results of optimal medical therapy as achieved in the COURAGE trial applicable to general clinical practice? The COURAGE trial investigators and patients are to be commended for exemplary compliance with medical therapies. However, recent registry data suggest that medical compliance, particularly with multiple concomitant medications is considerably less in the “real world” than was observed in the COURAGE trial. Indeed, at 1 year of follow-up, ~90% or more of the medically treated cohort in COURAGE was compliant with aspirin, statin, and beta-blocker therapies. This level of protocol-

driven polypharmaceutical compliance stands in contrast with a report from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry, where 46% of patients were compliant with beta-blocker alone, 36% with beta-blocker plus aspirin, and only 21% with beta-blocker, aspirin, plus lipid-lowering therapy in combination (41). Thus, beta-blocker therapy compliance rates of $\geq 86\%$ through 3 years of follow-up as observed in the COURAGE trial appear to be uncommon in clinical practice. A recent “real-world” international registry reported that 30% of medically managed patients with documented coronary artery disease received no lipid-lowering therapy and that compliance with guideline-recommended medical treatment was greater in patients with prior revascularization (PCI or coronary artery bypass graft) (42). Furthermore, medical noncompliance in clinical practice has been associated with increased mortality in late follow-up (43). Thus, the high rates of medical compliance as well as treatment to target levels for cholesterol, blood pressure, and glucose achieved in the COURAGE trial are exemplary but are not commonly reported from clinical practice registries. In this regard, clinical research nurse coordinators may provide a “case management” function not often available outside the confines of a randomized controlled clinical trial.

COURAGE in Perspective

What message(s) should the clinical practitioner derive from the COURAGE trial? First, in the context of precedent data (7–11) the COURAGE trial set an unrealistic goal: to show a 22% reduction in the already low annual rates of death and MI observed on aggressive medical therapy in stable coronary artery disease patients. The COURAGE trial does demonstrate a significantly better angina-free status as well as a reduction in the requirement for subsequent revascularization in those patients initially treated with PCI compared with medical therapy alone. Furthermore, these benefits were accrued by the PCI cohort with no penalty in terms of increased rates of death or MI. Second, the COURAGE trial appears to confirm earlier observations that incomplete revascularization of patients with multivessel disease may be associated with lesser degrees of clinical benefit and more frequent requirements for repeat revascularization (25–27). Third, despite “optimal” and possibly “unrealistic” (as applied in routine clinical practice) intensive medical therapy for stable coronary disease patients, severe or progressive anginal symptoms led to a surprisingly high rate (32%) of “crossover” to revascularization in patients initially assigned to medical therapy alone (no PCI). Fourth, the potential clinical benefits from DES combined with more complete coronary revascularization in multivessel disease patients would likely further enhance the magnitude and duration of antianginal benefit associated with the initial PCI strategy from what was observed in the

COURAGE trial. Fifth, because enrollment into the COURAGE trial occurred after coronary angiography and definition of the coronary anatomy, this valuable diagnostic and prognostic modality (angiography) should not be denied to patients with stable angina pectoris. Finally, medical and catheter-based therapies play at least complementary if not synergistic roles in the treatment of patients with atherosclerotic cardiovascular disease. The choice of therapy(s) for each individual patient must be made based on coronary anatomic suitability and in the context of the patient's lifestyle, functional capacity, level of symptom limitation, and their ability (physically, emotionally, and financially) to take the prescribed treatment. If PCI revascularization is performed, this procedure should be done using the most complete and effective tools and always in addition to (rather than in place of) medical therapies that reduce plaque progression.

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