COUNTERPOINT

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INTERPRETING THE COURAGE TRIAL

PCI is no better than medical therapy for stable angina? Seeing is not believing

Between the idea
And the reality
Between the motion
And the act
Falls the Shadow

—T.S. Eliot, The Hollow Men (1925)

PERCUTANEOUS CORONARY INTERVENTION (PCI) has improved considerably in the last 20 years, and so has medical therapy. With either, the nature and magnitude of clinical benefit depend, at least in part, on the clinical syndrome of the patient being treated.

See related introduction by Dr. Deepak Bhatt on page 618, and "point" article by Dr. William Boden on page 623.

In patients with ST-segment elevation myocardial infarction (MI)[1] or acute coronary syndromes without ST-segment elevation,[2,3] doing PCI (and as soon as possible) is better than medical therapy alone, as fewer patients will die or have another MI. However, in patients with stable coronary artery disease, the incidence of death or nonfatal MI is no lower with PCI than without it.[4–9]

As PCI has advanced from balloon angioplasty to bare metal stents to drug-eluting stents, angiographic and clinical restenosis rates have declined, as shown in randomized controlled clinical trials. Yet, in studies in patients with stable coronary artery disease, the rates of death or MI were no lower with drug-eluting-stents than with bare metal stents,[10,11] with PCI than with medical therapy,[4–9] or even with surgical coronary revascularization compared with medical therapy.[6,8,12–15]

Indeed, randomized controlled clinical trials and meta-analyses have consistently shown that PCI does not improve survival or reduce the incidence of death or nonfatal MI compared with medical therapy alone in patients with stable coronary artery disease.[4–9,12] In view of these findings, the major rationale for performing PCI in patients with stable coronary artery disease is to relieve anginal symptoms and to improve quality of life.

In stable coronary disease, PCI does not reduce deaths or nonfatal MIs

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial reaffirms the established premise that an initial management strategy of PCI using bare metal stents does not reduce the risk of death, MI, or other major adverse cardiovascular events when added to optimal medical therapy.[16] This observation is neither novel nor surprising.

To determine what, if any, implications the COURAGE trial should have for current clinical practice, let us first examine the premise, design, and execution of this trial.

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PROBLEMS IN THE TRIAL DESIGN

COURAGE's design had several problems: its hypothesis appears to have been unrealistic, it did not meet prespecified power assumptions despite protocol changes made after the trial was under way, and it defined periprocedural MI in a rather liberal way that placed PCI at a disadvantage.

Unrealistic hypothesis

Even though multiple earlier trials and meta-analyses found no differences in the incidence of death or MI with PCI than with medical therapy alone in patients with stable coronary artery disease, the central hypothesis of the COURAGE trial was that PCI would lead to a 22% lower incidence of death or nonfatal MI (the primary end point of this trial) than with medical therapy alone. Given the weight of prior randomized trial evidence, a noninferiority trial design may have been more appropriate.

Projected enrollment in COURAGE was initially set at 3,260 patients to accrue 614 primary end point events, based on a projected 21% rate of death or MI within 3 years in patients assigned to medical therapy without PCI. However, during the trial, possibly prompted by a low enrollment rate, the definition of MI was changed to include patients with elevated troponin levels, and the enrollment and follow-up periods were extended. Even so, only 413 end point events occurred (67% of the projected requirement), and the observed rate of death or MI through 3 years in medically treated patients was only 12%.

Projected rate of death or MI in COURAGE medical patients: 21% Actual rate: 12%

Inadequate statistical power

Thus, this trial was underpowered in the context of its original design assumptions. In addition, the use of death from any cause (vs cardiac-related death) in the primary end point may have obscured the trial's ability to differentiate between treatment strategies, as PCI would not be expected to reduce the rate of deaths due to causes other than heart disease. Interestingly, only 26.7% of all deaths in this trial were considered cardiac-related.

MIs were defined loosely

The definition of MI used in COURAGE included an enzymatic definition that specified only "positive results in cardiac biomarkers."[16] If the investigators counted any elevation of the creatine kinase-MB fraction (CK-MB) during or after PCI as an MI, then PCI would be disadvantaged, yet minor CK-MB elevations have little real prognostic importance (compared with a more conventional definition of at least three to five times the upper limit of normal).[17,18]

Possible selection bias

Patients were enrolled into the trial after undergoing coronary angiography. Therefore, those with more complex or severe stenoses may have been excluded, and the role of selection bias based on perceived angiographic risk cannot be determined. Evidence of a possible selection bias is that the annual cardiac mortality rate in the entire study cohort was relatively low—0.4%.

Moreover, the trial did not have a formal angiographic core laboratory analysis, making it difficult to interpret the angiographic procedural success rate, much less to accurately assess stenosis location and severity. Indeed, the procedural success rate (as assessed by the operator) was only 93% per lesion. Excluded from this analysis, inexplicably, were patients in whom the stenosis could not be crossed or in whom PCI was not attempted.

Another prospective assumption made by the authors was that only 10% of the medically treated patients would require revascularization during follow-up. Although about 80% of the patients had minimal or no angina on enrollment (Canadian Cardiovascular Society class II or less with a medium duration of 5 months), 32% of the medically treated group required revascularization for severe or progressive angina during follow-up.

Interestingly, the COURAGE patients had a very skewed distribution of anginal frequency (median of 3 and mean of 10 episodes weekly), which suggests there were two distinct patient populations. If so, this observation could explain why the crossover rate to PCI was so much higher than predicted—the subgroup with more frequent angina drove the number up.

PROBLEMS WITH HOW PCI WAS PERFORMED

To qualify for enrollment, COURAGE patients had to undergo angiography and have

at least one coronary vessel suitable for PCI with a proximal stenosis of at least 70%.

Did patients receive inadequate revascularization?

Even though about 70% of patients had at least two-vessel disease, only 36% of those assigned to PCI received more than one stent.

Multiple studies[19–22] have shown that partial or incomplete revascularization, whether by PCI or surgery, is associated with worse clinical outcomes (in particular, a greater need for repeat revascularization procedures) than is complete revascularization. This fact may, at least in part, explain the observation that 21.1% of the PCI patients in COURAGE required repeat revascularization (at an average follow-up of 10 months), although the investigators do not list how many of these additional procedures were performed for bare metal stent restenosis, remaining untreated stenoses, or progression of what was initially considered to be noncritical disease.

Few patients received drug-eluting stents

Nearly 1/3 of the medical patients in COURAGE eventually needed PCI

Only 2.7% of the COURAGE PCI patients received drug-eluting stents, as these devices were not available when the trial started. But in other randomized controlled trials,[11,23,24] rates of angiographic restenosis were, remarkably, 70% to 80% lower with drug-eluting stents than with bare metal stents, and rates of clinical restenosis were 50% to 70% lower. (However, the drug-eluting stents made no difference in the rates of death or nonfatal MI in these trials.)

In view of these findings, one could very reasonably hypothesize that a strategy of complete revascularization using drug-eluting stents in the COURAGE trial would have substantially reduced the need for repeat revascularization procedures and would have improved angina-free survival in patients assigned to PCI. Furthermore, although PCI patients reported better quality of life, less physical limitation, and less frequent angina at 3 years than medical patients, the benefit might have been even better with a strategy of complete revascularizaton using drug-eluting stents.

Possible worse PCI outcomes in VA hospitals

Another intriguing and potentially important observation from the COURAGE trial is that outcomes apparently differed depending on where patients were treated.

US patients treated outside of the US Veterans Administration (VA) system had a 29% lower rate of the primary end point with PCI than with medical therapy (15% vs 21%, respectively). (In US VA hospitals, the corresponding numbers were 22% with either therapy; and in the Canadian group, the numbers were 14% with medical therapy alone and 17% with PCI plus medical therapy.) Although too few non-VA patients were enrolled to allow for valid statistical comparison, this magnitude of difference would have satisfied the primary study hypothesis for superiority of PCI in reducing death or nonfatal MI.

The overall event rates were also different in Canada, where death or MI was observed in approximately 14% compared with 21 to 22% of patients enrolled in the United States. This discrepancy suggests that significant differences in disease severity existed, but it remains unexplained.

Thus, both incomplete revascularization using bare metal stents and possibly worse outcomes after PCI in VA hospitals may have contributed to the outcomes of the COURAGE trial. Similar issues arose in the VA Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, in which PCI was not more beneficial than medical therapy for patients with non-ST-segment-elevation acute coronary syndromes.[25] The results of the VANQWISH trial remain at odds with the weight of evidence from the randomized controlled clinical trials[2,3] and with the current American College of Cardiology/American Heart Association Class 1 guideline recommendation for early angiography and revascularization in patients who present with non-ST-segment-elevation acute coronary syndromes and high-risk indicators.[26]

MEDICAL THERAPY WAS BETTER THAN IN THE REAL WORLD

The COURAGE investigators and patients are to be commended for exemplary medical

compliance and adherence to treatment targets. Indeed, such protocol-driven compliance with multiple medications may not be achievable in routine medical practice.

For example, although compliance with three medications (aspirin, statins, and beta-blockers) averaged 90% or more through 3 years of follow-up in COURAGE, recent data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) registry suggest that as few as 21% of patients comply with these three therapies after non-ST-segment-elevation acute coronary syndromes.[27]

Similarly, data from managed care organizations suggest that as few as 46% of patients remain compliant with beta-blocker therapy at 1 year after an MI.[28]

An international registry recently reported that 30% of patients with documented symptomatic coronary artery disease received no lipid-lowering therapy and that compliance with guideline-recommended therapies was significantly greater in patients with prior revascularization.[29] Although 70% of COURAGE patients achieved a low-density lipoprotein cholesterol (LDL-C) level lower than 85 mg/dL, fewer than 50% of patients in CRUSADE achieved an LDL-C level lower than 100 mg/dL.[27]

Remarkably, 65% of COURAGE patients achieved the systolic blood pressure target (less than 130 mm Hg) and 94% achieved the diastolic target (less than 85 mm Hg); 45% of diabetic patients achieved a glycosylated hemoglobin level of 7.0% or less.

These observations raise questions about whether the intensive medical therapy given in the COURAGE trial can be replicated in routine clinical practice.

IMPLICATIONS FOR CLINICAL PRACTICE

What implications should the COURAGE trial have for clinical practice?

- The failure of PCI in the COURAGE trial to meet the hypothesized, aggressive, and unrealistic primary end point of a 22% lower rate of death or nonfatal MI compared with medical therapy in patients with stable coronary artery disease is consistent with the findings of prior randomized controlled clinical trials and is neither surprising nor new. Of note, however, is that the risk was 29% lower with PCI than with medical therapy in COURAGE patients who were treated outside of the US VA hospital system.
- Incomplete revascularization in patients with multivessel disease using bare metal stents leads to more repeat procedures and recurrent angina. More complete revascularization using drug-eluting stents has been as clinically beneficial (reducing the rates of repeat revascularization and recurrent angina) as surgical coronary revascularization, but definitive comparisons await the results of ongoing randomized trials.
- Despite comprehensive medical therapy, many (32%) of patients in the COURAGE medical therapy group eventually needed PCI because of severe or progressive angina symptoms.
- Patients were enrolled into the COURAGE trial following coronary angiography, and this diagnostic and prognostic evaluation should not be denied to our patients who present with stable coronary disease. Foregoing angiographic definition of coronary anatomy would also preclude the detection of left main or severe three-vessel coronary disease.
- Medical and catheter-based therapies play complementary roles in the treatment of patients with stable coronary artery disease. The choice of therapy or therapies must be made for each patient on the basis of anatomic suitability as well as the patient's ability to take the prescribed treatment.

If medical therapy is initially chosen, aggressive treatment to therapeutic targets and medical compliance must be achieved. Conversely, if PCI is chosen, complete revascularization should be done using the most effective technology (drug-eluting stents), and the patient should also receive medical therapies aimed at reducing plaque progression. ■

Medical therapy and PCI play complementary roles in stable coronary artery disease

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