Percutaneous Coronary Intervention for Stable Patients: Is There any Benefit Beyond Symptom Relief?

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Abstract

The indications for percutaneous coronary intervention (PCI) continue to evolve because of the steady improvement in technology, broadened patient and lesion selection criteria, and new evidence from clinical trials. Considerable controversy was generated by the main results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which no difference in long-term outcome was reported for stable patients with coronary disease randomized to an initial strategy of PCI plus optimal medical therapy *versus* optimal medical therapy alone. In patients with chronic stable angina, medical therapy remains the cornerstone and should be optimized for all patients, while the major achievable goals of PCI are to affect symptoms, either by decreasing or preventing them, reducing the need for subsequent procedures and relieving ischemia. In patients with stable coronary artery disease, however, no reduction in death or myocardial infarction has been observed, and these limitations of PCI in this clinical setting need to be emphasized. The message from the COURAGE trial may be refined based on recently presented nuclear and angiographic sub-studies, such that patients with substantial residual ischemia on optimal medical therapy should be considered for crossover PCI, as it is associated with greater likelihood of death and myocardial infarction. However, those findings need to be confirmed by prospective evaluation before being widely accepted by the interventional community.

Introduction

A large body of evidence, based on multiple prospective randomized clinical trials (RCTs), supports the survival benefit of revascularization over medical therapy in several patient subsets. In high risk patients, such as those with ST-elevation myocardial infarction (STEMI), as well as in non-STEMI patients and those with unstable angina, accumulated clinical evidence provides strong support that PCI is the preferred strategy for improving patient outcome, both in terms of morbidity as well as mortality. In patients with stable coronary artery disease (CAD), revascularization was believed to be superior based on the assumption that high-risk coronary anatomy or myocardial ischemia increases the risk of future death and myocardial infarction ("conventional wisdom" that the triad of angina, objective evidence of myocardial ischemia, and the presence of ≥1 flow-limiting coronary stenoses necessitated revascularization). Major advances in our understanding of the pathophysiology of acute coronary syndrome (ACS) and the recognition of the significance of predisposing non-flow-limiting coronary stenoses prone to rupture, has led to the more aggressive use of appropriately targeted pharmacologic agents and the evolution of what constitutes optimal medical therapy (OMT). Until recently no "strategy trial" had been conducted to support the concept that in patients with stable CAD, a therapeutic strategy combining OMT with mechanical intervention compares favorably with OMT alone. Few recent clinical trials have generated as much intense interest (and controversy) as the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial published in the spring of 2007 in the *New England Journal of Medicine*[1]. As it is well known, the COURAGE trial set out to evaluate the relative merits of optimal medical therapy (OMT) *versus* the combination of OMT plus PCI in patients with stable coronary artery disease. It was a multicenter randomized clinical trial, which screened 35,539 patients, but randomized only 2,287 patients who fulfilled entry criteria that included objective evidence of myocardial ischemia and stable symptoms. An important point is that all patients enrolled in the trial underwent screening angiography. All patients had chronic stable angina class I-III (Canadian Cardiovascular Society Class 0/1 angina was present in 42-43% of all patients), with AHA/ACC class I or II indication for PCI with at least 1 proximal vessel involved and objective evidence of ischemia by ECG, perfusion scintigraphy, or echo stress testing. The lesions were graded as > 70% luminal diameter stenosis by operator's visual estimation. Each group had > 30% incidence of proximal LAD stenosis. Excluded were patients with persistent class IV angina, a markedly positive stress test, resting ST-T wave abnormalities, refractory heart failure, shock or left ventricular ejection fraction < 30%, revascularization within the previous 6 months, and coronary anatomy not suitable for PCI. At baseline, many patients were already at

Key words

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the target levels for lipids, blood pressure and diabetic control that were recommended by current guidelines[2].

The COURAGE trial is an example of clinical trial often missing in the current clinical scenario - the comparative effectiveness studies - and the results were stunning. The primary endpoint was all-cause mortality and nonfatal myocardial infarction (MI) during a follow-up period of at least 2.5 years. After a mean of 4.6 years, the cumulative primary event rates were 19.0% for the PCI plus OMT group and 18.5% for the OMT alone group (hazard ratio [HR] 1.05, 95% CI, 0.87–1.27, $P = 0.62$) (the PCI + OMT group had 211 events and the OMT group had 202 events). The mortality rate for PCI+OMT was 5.9% and for OMT alone, 6.5%. The rates of MI were 9.4% for PCI+OMT and 10.4% for OMT. The cumulative endpoints (including CVA) were 20% for PCI+OMT and 19.5% for OMT. Freedom from angina was initially higher in the PCI+OMT group, but at the end of 4.6 years the OMT group was as equally free of angina. It is unclear whether this improvement in the OMT patients was a result of cross over to PCI or development of collateral vessels. However, it needs to be reiterated that 6% of PCI+OMT patients never underwent PCI, 14.5% of lesions were treated with balloon only and 31.1% of the OMT patients crossed over to PCI. Furthermore, only a small number of patients in the PCI+OMT group (2.7%) were treated with now standard interventional therapy, drug-eluting stents and 12 months of dual antiplatelet therapy. Perhaps, the least controversial singular achievement in the COURAGE trial is the profound impact that intensive OMT and lifestyle intervention had on mitigating clinical events in both randomized arms of the trial during long-term follow-up. Although no study is perfect, the COURAGE trial was professionally carried out by the investigators and study findings have been extensively circulated and quoted and formed the basis for the study conclusions that, as the initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy[3-7]. Consequently, the data have been used by some authors to suggest that there is an inherent limitation in the efficacy of percutaneous coronary revascularization. Other clinicians have used the results to support their conclusions that revascularization is over utilized. According to industry and media sources, after COURAGE publication, the number of PCI procedures performed in the United States decreased by about 10% to 15%, as many physicians integrated these findings to their clinical practices[8]. Although there has been much criticism of COURAGE, including the randomization after the angiography selecting a low risk subset, there are several issues that need to be reiterated, particularly regarding the study design and the selection of endpoints. A group of very prominent interventional cardiologists wrote a viewpoint editorial in the *Journal of the American College of Cardiology,* highlighting the weaknesses and limitations of the COURAGE trial[9]. They stated that the COURAGE investigators set an unrealistic goal: to demonstrate a 22% reduction in the already-low annual rates of death and MI observed in patients treated with aggressive medical therapy. They mentioned that, together with the low prevalence of the use of drug-eluting stents, incomplete revascularization may have contributed to the 21% rate of additional revascularization in this group at a mean of 10 months of follow-up. Furthermore, these authors stated that the information from the COURAGE trial is not new or surprising. Table 1 in their Editorial cites 7 prior published trials, showing no difference in mortality and MI rates in patients randomized to PCI *versus* medical therapy for stable CAD. A recent meta-analysis of 17 randomized trials on the value of a PCI-based treatment strategy in 7513 patients with stable coronary artery disease even goes a step further, by demonstrating that a PCI-based treatment strategy is associated with a 20% reduction in the OR of death when compared with a medical treatment-only strategy[10].

Is there any benefit of PCI in patients with stable angina beyond symptom relief?

The evidence-based message concerning patients with chronic stable angina is clear and consistent: 1) revascularization is associated with greater symptomatic relief, but there are no differences regarding the "hard" endpoints of death and MI; and 2) in patients on medical therapy, crossover to revascularization is frequent. Holmes et al[11] recently proposed several explanations for the lack of benefits of PCI in the COURAGE trial and other trials in reducing death or MI: 1) Cardiac mortality rates in patients with stable angina in the current era are low; 2) It is possible that drug therapy and secondary prevention improve endothelial function and stability over the long term; 3) The potential benefits of PCI in the culprit lesion or lesions are diluted by the effects of disease progression in other vessels or the failure to provide complete revascularization initially; 4) In patients with severe stenoses that are treated medically, collateralization may play a role in alleviating symptoms, although collaterals are generally an indication of severe ischemia; 5) Acute coronary syndrome, secondary to ruptured plaques, frequently occurs at sites apart from areas of severe stenosis, regardless of initial PCI. This observation is also true for patients receiving optimal medical therapy alone[11].

Therefore, the appropriate rates of PCI use are a major concern, with important socioeconomic implications. It is necessary to establish whether its use is appropriate, and, if not, why this is so. It is up to the cardiovascular community to ensure that evidence-based medicine dominates clinical practice.

Previous RCTs have demonstrated that patients with extensive CAD preferentially benefited from revascularization, whereas patients with smaller amounts of the disease did not[12-14].

In a retrospective analysis of 10,627 patients who underwent adenosine myocardial perfusion stress imaging and had no previous myocardial infarction or PCI, Hachamovitch et al[15] identified an ischemic threshold of 12.5%, above which the survival benefit for revascularization over medical therapy increased progressively as a function of increased levels of inducible ischemia[15]. In the setting of no or mild amounts of inducible ischemia (<12.5%), patients who underwent medical therapy had a survival advantage over those who underwent PCI, whereas above that threshold, outcome was better for PCI. Because the prognosis of a stenosis in the coronary vascular bed depends more on function than on anatomic extent, we wonder whether "optimal" medical

therapy could remain non-inferior to PCI, even at higher levels of ischemic burden. Soares et al[16], in the MASS II sub-analysis, compared 5-year outcomes of patients with stable multivessel coronary disease randomized to surgery, angioplasty, or medical treatment and demonstrated that the initial therapeutic approach did not modify the mortality trend during 5 years for nondiabetic subjects with stable multivessel coronary disease. Moreover, the treatment modality did not influence the outcomes during the first year in diabetic subjects. However, from the first year and afterward, diabetic subjects undergoing treatment with invasive strategies (angioplasty or surgery) had significantly improved mortality rates in comparison with patients randomized to a more conservative medical strategy[16].

Data continues to accrue from the COURAGE trial, which sheds more light on the role of PCI in stable coronary artery disease. An important substudy of the COURAGE trial was the nuclear study, which compared the magnitude of change in ischemic burden following treatment with PCI plus OMT *versus* OMT alone[17]. There were 159 patients in the combined PCI/OMT group and 155 in the OMT only group (314 patients in total) who had documented ischemia before treatment and then underwent a repeat myocardial perfusion study at 6-18 months. The timing of 6-18 months was chosen to avoid the window of in-stent restenosis as a confounding factor. These patients only comprised 14% of the total COURAGE population, and the prognostic analyses were underpowered. However, there were no statistically significant differences between the two groups in terms of angina severity (cardiovascular society Class 1 or 2, which occurred in 73% and 74%), two or three-vessel disease, with ejection fraction of 57-58%. The percentage of ischemic myocardium at baseline for these patients was approximately 8.4%. One third of the patients who underwent stress perfusion imaging had 10% or more of the myocardium rendered ischemic at baseline. As it might have been predicted by prior observational studies published in the literature, the greatest therapeutic benefit was seen in those patients with the most severe baseline ischemia (the percentage of patients with ischemia reduction ≥ 5% of the myocardium was in 33% of the PCI group *versus* 19.8% in the optimal medical therapy group, P = 0.0004). In those patients with moderate to severe ischemia at baseline prior to treatment, 78% had a reduction in ischemia with PCI+OMT *versus* 52% in the optimal medical therapy group (P = 0.007). The ability of PCI to reduce the ischemic burden was also tested in a randomized comparative study between CABG and PCI in equivalent ischemic situations at scintigraphy and the study demonstrated that the strategies did not differ significantly in reducing the myocardial ischemic load 6 months after the procedure[18].

The most important follow-up consideration is the clinical effect of ischemia reduction, as patients with ischemia reduction had a lower death or myocardial infarction risk. For all the patients combined in the nuclear COURAGE sub-study, the death or MI rate was 13.4% in patients who had a 5% ischemia reduction or greater *versus* 24.7% in patients with no reduction in inducible ischemia at the follow-up study. Death or myocardial infarction rates ranged from 0% for patients with no residual ischemia to 39% in patients with 10% residual ischemia on the follow-up stress test. These results show a trend in the same direction as the Angioplasty Compared with Medicine Study, an older study reporting that ischemia normalization was associated with improved event-free survival in long-term follow-up[19]. This supports the importance of the recognition and treatment of ischemic burden rather than just anatomy as the goal of interventional therapies. At present, it may be prudent to consider PCI + OMT at the outset for patients with a 10% ischemic burden or greater, because this combination was more effective in reducing ischemia (and improving angina) than OMT alone. Stable patients with mild, minimal, or no inducible ischemia on stress imaging can safely be treated with OMT and would cross over to PCI after clinical indications.

An angiographic substudy from the COURAGE trial also revealed similar conclusions[20]. Authors hypothesized that more severe angiographic coronary artery disease, and depressed ejection fraction would identify higher risk patients with improved outcome from the PCI + OMT group, when compared with the OMT alone. It was demonstrated that the increased number of stenotic vessels (hazard ratio [HR] 1.44, 95% CI, 1.27–1.64, $P< 0.001$), and reduction in ejection fraction (hazard ratio [HR] 1.49, 95% CI, 1.18–1.90, $P = 0.001$) identified patients at greater risk of death and MI.

In addition, another COURAGE substudy reported worse clinical outcomes of initially optimal medically-treated COURAGE patients who crossed over to coronary revascularization compared to those managed with OMT alone[21]. Hypercholesterolemia, 3-vessel disease and a greater burden of angina were all associated with a need for cross over in the COURAGE OMT patients. Fully adjusted outcome models suggested no difference in mortality, but higher rates of nonfatal MI (hazard ratio [HR] 6.7; 95% CI, 4.4-10.3) and worse 1-year SAQ Angina (81.3 *vs* 85.2), physical limitation (71.3 *vs* 73.8) and Quality of Life (71.7 *vs* 73.8) scores ($p<0.0001$ for all) in crossed over patients vs. those treated with OMT alone. According to the authors, identifying patients that are likely to need upfront revascularization may minimize the period during which such patients present worse health status.

Taken together, data from three post-hoc COURAGE substudies suggest that higher risk patients with chronic stable angina benefit from PCI and as a result, may have subsequent reduction in hard clinical events, death or myocardial infarction. However, these findings need to be confirmed by prospective evaluation before their wider acceptance by the interventional community.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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