“Does percutaneous coronary intervention (PCI) reduce mortality among patients with stable coronary artery disease?” Very few questions have been so hotly debated within the medical literature over the past decade. Invasive treatment with PCI has figured prominently in the treatment of patients with coronary artery disease, with >1.3 million PCIs performed in the United States in 2005.1 The rapid growth in PCI as a viable alternative to medical therapy or coronary artery bypass graft (CABG) surgery was catalyzed initially by the aesthetic appeal of this less invasive procedure to improve flow in the coronary arteries and was subsequently reinforced by the improved ease and safety of PCI. Proponents of PCI argue that improved blood flow leads to reduced ischemic substrate and improved overall prognosis,2 whereas opponents claim that patients with stable coronary artery disease have coronary plaques that are less likely to result in an acute coronary syndrome.3 Therefore, intervening focally on a coronary lesion via PCI is unlikely to alter their overall prognosis.

This conclusion has been supported by earlier meta-analyses and by the recently published Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study, the largest trial to date to address whether PCI is beneficial as compared with medical therapy among patients with stable coronary artery disease.4,5 The authors concluded that PCI was not associated with a reduction in death (summary odds ratio [OR] of 0.94; 95% CI, 0.72 to 1.24; Figure).4

As the trials included in this systematic review enrolled patients from 1987 to 2001, there was a concern that they did not reflect contemporary practice in patients with coronary artery disease. For example, the Second Randomized Intervention Treatment of Angina study was the largest trial in the Katritsis’s review that enrolled 1018 patients with a median follow-up of 7 years.5 The Second Randomized Intervention Treatment of Angina investigators found an early hazard associated with coronary angioplasty with an increased frequency of death or myocardial infarction (6.3% in the angioplasty arm versus 3.3% in the medical arm) from procedure-related complications.6 However, in Second Randomized Intervention Treatment of Angina, coronary stent use was limited to 9% of PCI patients, and <20% of enrolled patients were prescribed an angiotensin-converting enzyme inhibitor or a statin medication.5,6 The safety of PCI has likely improved substantially in the interim with the widespread use of coronary stents, which have markedly reduced the frequency of periprocedural complications. Similarly, medical therapy had also progressed tremendously, further questioning the generalizability of these results. A pressing need emerged for a large, contemporary, randomized trial designed specifically to address this question.

Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation

Accordingly, COURAGE was designed to address these identified weaknesses by comparing the contemporary practice of PCI with optimal medical therapy. A total of 2287 patients were enrolled and followed for a median duration of 4.6 years.3 In contrast with earlier trials, 94% of PCI patients in the COURAGE study had coronary stents during their procedure, with utilization of angiotensin-converting enzyme inhibitor and statin medications at 64% and 91%, respectively.3 The authors of COURAGE concluded that “PCI did not reduce the risk of death, myocardial infarction, or other major cardio-

Evidence Before COURAGE

Before the COURAGE trial, Katritsis and Ioannidis4 performed a meta-analysis of relevant trials comparing coronary angioplasty with and without coronary stenting to medical therapy in patients with stable coronary artery disease. In total, their meta-analysis included 2950 patients enrolled in 11 randomized studies.4 The authors concluded that PCI was not associated with a reduction in death (summary odds ratio [OR] of 0.94; 95% CI, 0.72 to 1.24; Figure).4

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vascular events when added to optimal medical therapy, as they found no significant difference in mortality (OR, 0.87; 95% CI, 0.65 to 1.16) or myocardial infarction (OR, 1.13; 95% CI, 0.89 to 1.43).

Although COURAGE was designed to provide definitive knowledge in this area, it has also come "under fire" in many forums as to the generalizability of the results to patients treated in routine clinical practice. Those critical of the COURAGE study have identified issues including its highly restrictive recruitment strategy, unrealistic levels of medication compliance, high crossover rates, and suboptimal PCI techniques. In response, equally persuasive arguments have been made as to the strength of the COURAGE trial. Irrespective of the debate surrounding it, COURAGE remains the single largest and most contemporary study in this area to date. Importantly, adding the results of COURAGE to the meta-analysis by Katritsis and Ioannidis did not alter the estimate of PCI on mortality (Figure).

**Meta-Analysis by Schönig et al: PCI Saves Lives?**

Given the consistency of findings among earlier studies, the results of the meta-analysis by Schönig et al came as a surprise. The authors summarized 17 trials involving 7513 randomized patients and suggested, for the first time, that PCI may be lifesaving among patients with coronary artery disease. PCI was associated with a significant reduction in death (OR, 0.80; 95% CI, 0.64 to 0.99) and nonsignificant reductions in cardiac death (OR, 0.74; 95% CI, 0.51 to 1.06) and myocardial infarction (OR, 0.90; 95% CI, 0.66 to 1.23; Figure). As expected, this article has attracted substantial media attention and may be embraced by practicing clinicians.

**Should PCI Patients Be Mixed With Patients With CABG?**

Although the intention of the study by Schönig et al. was to evaluate the efficacy of PCI, the investigators included 4 trials (2071 patients) representing 27.6% of the meta-analysis population that compared an invasive strategy (PCI or CABG) with medical therapy. Rates of CABG ranged from 20% to 41% in these studies. Because of the lack of individual-level data, the authors were forced to assume that the outcomes observed in the invasive-strategy arm were attributable entirely to PCI (i.e., outcomes from PCI and CABG were treated as outcomes of PCI). Although the estimates in these 4 trials were similar to the overall study estimates, their inclusion increased the overall power of the meta-analysis and potentially blurred the original intent of comparing PCI and medical therapy due to the inclusion of the CABG cases (Figure).

**Influence of Stable Versus Unstable Coronary Artery Disease Patients**

The distinction between stable versus unstable patients is important in evaluating the possible benefit of PCI, as it has been consistently demonstrated to be beneficial compared to medical therapy among patients with acute coronary syndrome. Systematic reviews of randomized trials evaluating primary PCI for patients with ST-segment–elevation myocardial infarction have demonstrated absolute reductions of 2% for mortality and 4% for myocardial infarction compared with fibrinolytic therapy. Even among ST-segment–elevation myocardial infarction patients who were successfully treated with fibrinolytic therapy, recent evidence has suggested that PCI is associated with a mortality reduction comparable with medical therapy. Similarly, several landmark studies have demonstrated the benefit of PCI in reducing hard outcomes among patients with non-ST–elevation myocardial infarction. Therefore, systematic reviews evaluating stable coronary artery disease that include a relatively high proportion of acute coronary syndrome patients would likely overestimate the benefit of PCI.
As was the case in previous meta-analyses, Schömig et al included patients who were stabilized after recent myocardial infarction. Four trials enrolling 1557 patients with recent myocardial infarction (<4 weeks), which made up ~20% of patients, were included in the meta-analysis. In addition, the Swiss Interventional Study on Silent Ischemia Type II study restricted its enrollment to patients with a myocardial infarction within the preceding 3 months and evidence of ischemia. In these 5 trials of recent myocardial infarction, PCI was associated with substantial reduction in death as compared with medical therapy (OR, 0.51; 95% CI, 0.27 to 0.96). If these trials were also excluded from the analysis, there is no longer any difference between PCI and medical therapy for the risk of death (OR, 0.91; 95% CI, 0.74 to 1.12), with essentially the same point estimate as that of the COURAGE trial (Figure).

Are We Really Comparing Apples and Oranges?
Coronary artery disease represents a spectrum that ranges from asymptomatic patients with nonobstructing lesions, to patients with stable angina with flow-limiting lesions causing ischemia, to patients with unstable acute coronary syndromes where disruption of vulnerable or high-risk plaques act as a stimulus for thrombogenesis. The clear delineation of when a patient with an acute coronary syndrome becomes stable is potentially difficult, as patients may undergo this transition rapidly. Even in the COURAGE trial, enrollment criteria included patients who were stable after myocardial infarction (without specifying the duration of stabilization) in addition to patients with chronic angina pectoris (Canadian Cardiovascular Society class I to III) and asymptomatic patients with objective evidence of myocardial ischemia.

The presence of heterogeneity in meta-analysis is frequently assessed by the Cochran Q statistic, and the proportion of variability due to heterogeneity between individual trials is frequently quantified by the I² index. Although we have illustrated that substantial differences were observed in terms of patient selection and results of individual trials in the study by Schömig et al, the investigators did not find significant statistical heterogeneity. This highlights the fact that tests for statistical heterogeneity are often underpowered, and readers should ensure that trials are appropriately selected even in the situation when statistical heterogeneity is absent.

Summary
A fundamental principal of meta-analyses is that the same research question on a similar patient population is being addressed in all the enrolled studies. On the basis of our review of the identified studies, we concluded that the divergent findings on the potential mortality benefit of PCI in patients with stable angina are likely due to differences in characteristics of the patients enrolled in the studies. Among patients with chronic stable angina that is not immediately after myocardial infarction, the totality of evidence still favors the conclusion that PCI does not reduce mortality.

In fact, whether PCI improves quality of life among patients with stable coronary angioplasty is being questioned, as emerging data from a substudy of the COURAGE trial suggest PCI is associated with only a modest improvement in quality of life, which actually dissipated over time. Once again, clinicians are being challenged to understand why a divergence exists between recent evidence and the conventional wisdom that PCI is associated with a large benefit in symptom relief. Is it due to greater success in optimizing medical therapy, or is it due to a fundamental change in the type of patients who undergo PCI in current practice? Are there any demographic, clinical, or procedural characteristics that will ensure undergoing a PCI will improve a patient’s quality of life and other outcomes? Rather than perseverating over the question of whether PCI improves mortality, an understanding of these differences may aid in the appropriate use of interventional PCI practice, especially in light of rapidly escalating healthcare costs.

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