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Reexamining the Efficacy and Value of Percutaneous Coronary Intervention for Patients With Stable Ischemic Heart Disease

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Abstract

Percutaneous coronary intervention (PCI) continues to be performed frequently for patients with stable ischemic heart disease, despite uncertain efficacy. Individual randomized trial data and meta-analyses have not demonstrated that PCI in addition to optimal medical therapy reduces the incidence of death or myocardial infarction in patients with stable disease. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial did not show benefit for cardiovascular outcomes or mortality but did find a modest improvement in quality of life that did not persist at 3 years. Long-term follow-up from COURAGE (up to 15 years) found no differences in mortality, consistent with other published literature. How PCI could reduce long-term mortality or prevent myocardial infarction is not clear because sites of future plaque rupture leading to myocardial infarction are unpredictable and PCI can only treat localized anatomic segments of obstructive atherosclerosis. In addition, PCI is expensive, and the value to society of PCI for stable disease has not been demonstrated. The ISCHEMIA trial will assess the role of PCI for stable ischemic heart disease using newer technology and in patients with greater ischemic burden than in COURAGE. After nearly a decade, the COURAGE trial and other studies have given us pause to critically reexamine the role of PCI for patients with stable ischemic heart disease. Until further research can show that PCI can reduce cardiovascular events in these patients, a first-line strategy of optimal medical therapy is known to be safe, effective, and noninferior to PCI, and our practice should more closely follow this strategy.

> A wise man, therefore, proportions his beliefs to the evidence.
>
> David Hume, An Enquiry Concerning Human Understanding, 1748[1]

Health care delivery in the United States is undergoing considerable change, with an increasing focus on quality and value of care, defined as “safe, effective, patient-centered, timely, efficient, and equitable.”[2] (p3) An important part of developing an optimal healthcare system is to include assessment of the effectiveness and value of therapies.[3] The treatment of stable ischemic heart disease with percutaneous coronary intervention (PCI) provides an

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excellent case study in which despite high utilization there is scant supportive evidence to justify the high costs of such use.

Percutaneous Coronary Intervention: A Brief Synopsis

Since the introduction of balloon angioplasty in 1977, there have been multiple improvements, including the introduction of bare-metal coronary stents in 1994, drug-eluting stents in 2004, and greater control of stent thrombosis with dual antiplatelet therapy.[4–7] Continuing improvements in methods have dramatically lowered rates of complications, but they still occur.[8] The efficacy of PCI in patients with ST-elevation and non–ST-elevation myocardial infarction (MI) has been demonstrated in randomized trials.[9,10] The studies comparing the efficacy of PCI and coronary artery bypass graft surgery (CABG) generally favor CABG, especially in patients with diabetes and/or extensive multivessel coronary artery disease.[11,12] Data demonstrating the efficacy and value of PCI compared with medical therapy for patients with stable ischemic heart disease in prolonging life or preventing MI have been minimal to date.[13–15]

Rationale and Principal Findings From COURAGE

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial was published in 2007 and provided considerable new data concerning the efficacy and value of PCI in patients with stable ischemic heart disease.[16] It was a randomized trial that prospectively tested 2 initial management strategies of PCI with intensive medical therapy vs medical therapy alone, in 2287 patients with stable ischemic heart disease who had 1 or more angiographically severe (≥70%) coronary stenoses and noninvasive evidence of inducible myocardial ischemia. A critical design feature of COURAGE was equal application of guideline-driven optimal medical therapy to both study arms.[16,17] The primary end point was all-cause mortality or nonfatal MI. Ata median 4.6 years of follow-up, there was no difference in the primary outcome between the 2 treatment groups.

There was improved quality of life in the PCI arm, as measured with the Seattle Angina Questionnaire.[18] However, the benefit was modest, did not persist beyond 3 years, and varied by specific health status domains. For the physical limitation domain, the percent of patients with a clinically significant improvement at 6 months was 51% with PCI vs 42% with medical therapy alone ($P < .001$), but at 3 years this was 45% vs 47% ($P = .50$).[18]

Percutaneous coronary intervention also did decrease ischemia to a greater extent than medical therapy alone.[19] However, this did not translate into improvement in clinical outcomes. When patients were stratified by these verity and extent of ischemia into those with “no to mild” ischemia compared with “moderate to severe” ischemia, there was no significant decrease in cardiac events with PCI in either stratum.[20] Only a minority of patients in COURAGE had moderate to severe ischemia.[20]

The COURAGE trial has been criticized for the quality of the PCI procedures and for not being broadly generalizable to contemporary practice.[21] However, there was no evidence of substandard PCI procedures, and the patients in COURAGE have been shown to be

comparable to those in other populations with stable disease.[22] They had a mean frequency and duration of angina of 6 episodes per week and 23 months, respectively; 67% had hypertension, 71% dyslipidemia, 34% diabetes, 29% current smoking, 39% prior MI, 25% prior revascularization, 85% inducible ischemia with a high proportion having multiple reversible perfusion defects, 69% multivessel coronary artery disease, and 68% left anterior descending disease.[16,17] This was an intermediate- to high-risk cohort with an annualized rate of death or MI of 4.1%. Thus, COURAGE is actually typical of the cohort of patients currently receiving PCI for stable ischemic heart disease.

Other Randomized Trials: BARI 2D and FAME 2

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, 2368 patients with type 2 diabetes and obstructive coronary artery disease were randomized to revascularization with intensive medical therapy vs intensive medical therapy alone.[23] Patients were stratified to PCI or CABG as the appropriate intervention and randomized to revascularization or medical therapy within those strata. There was no difference in survival or freedom from the composite of death, MI, or stroke between the randomized groups overall or within the PCI stratum at 5 years.

In the Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2 (FAME 2) study, 888 patients of a planned 1600 participants were randomized to fractional flow reserve (FFR)-guided PCI plus best available medical therapy vs medical therapy alone.[24] The primary end point was a composite of death, MI, or urgent revascularization during a projected median 2-year follow-up. The trial was stopped prematurely (after a median follow-up of only 7 months) because of a difference favoring FFR-guided PCI. However, this was entirely driven by a difference in urgent revascularization. There was no difference for the other components of the primary end point of MI (n = 56) or death (n = 14) from any cause.[24,25] Because this trial was not powered to assess effects on MI or death because of the premature stoppage, the residual question is whether the observed difference in urgent revascularizations is sufficient to justify routine use of FFR-guided PCI in patients with stable ischemic heart disease.

Meta-analyses

There have been several meta-analyses, both before and after the publication of COURAGE, which have shown similar results.[13,15] Of particular interest was the meta-analysis by Stergiopoulos et al,[15] which included 4064 patients with stable ischemic heart disease from 5 trials, principally COURAGE, BARI 2D, and FAME 2, all of which enrolled patients with objective evidence of ischemia. The central finding was the absence of benefit from PCI on any clinical end point (including death, MI, need for revascularization, and even angina relief).

The American College of Cardiology developed appropriate use criteria for PCI, which require evidence of ischemia by noninvasive testing or FFR plus an attempt at medical therapy with atleast 2 anti-anginal agents before performing PCI for stable ischemic heart disease.[26] The recognition that PCI has not been shown to reduce cardiovascular events,

together with the introduction of appropriateness criteria in patients with stable ischemic heart disease, has been associated with a 25% decline in the rate of PCI use for such patients in the United States between 2006 and 2010.[27–29] However, in 2010 there were still 500 000 PCI procedures performed in the United States, of which perhaps half were for stable disease.[29]

Could PCI for Stable Ischemic Heart Disease Reduce Mortality?

In the original COURAGE publication, there was a nonsignificant finding of reduction in total mortality with PCI (7.6% vs 8.3%), yielding a 13% (hazard ratio, 0.87; 95% CI, 0.65–1.16) relative risk reduction at 7-year follow-up, although the survival curves of the 2 groups were largely superimposed until the last 1 year.[16] It was recognized on publication that then on significant finding of lower mortality with PCI might be spurious as the number of deaths was small in the last year of observation. The meta-analysis by Stergiopoulos et al[15] similarly found a nonsignificant 10% (odds ratio, 0.90; 95% CI, 0.71–1.16) relative reduction in mortality with PCI. However, Stergiopoulos et al conducted their meta-analysis prior to the recent extended follow-up of COURAGE, with mortality ascertainment upto 15 years.[30] In this analysis, there were 561 deaths, compared with 180 deaths in the original COURAGE report, permitting greater precision of the estimation of survival in each group, and revealing essentially superimposed survival curves in the PCI plus optimal medical therapy and optimal medical therapy alone arms throughout follow-up (Figure 2 in Sedlis et al[30]). Furthermore, there was no suggestion of a PCI survival benefit in any subgroup, including patients with moderate to severe ischemia.

Theoretical Mechanism(s) for a PCI-Related Mortality Reduction

What are the theoretical mechanisms by which PCI might decrease mortality or prevent MI in patients with stable disease? First, some have conjectured that it could reduce mortality by stabilizing vulnerable plaques.[31,32] Another hypothesis is that PCI could reduce exercise-induced ischemia, and consequently sudden cardiac death. However, the competing argument is that we know from multiple studies that the coronary plaques most vulnerable to rupture or erosion—leading to a subsequent cardiac event—are often not angiographically obstructive lesions, which would be the primary target of PCI. Indeed, patients may have multiple vulnerable plaques, most of which are not severe angiographically and hence not targets for PCI.[33–35]

Findings from the PROSPECT study likewise support the observation that most coronary events in patients who have previously undergone stent placement emanate from new plaque ruptures, not from stented coronary segments.[35] Finally, despite years of intensive research, we have limited ability to reliably identify those coronary plaques, either invasively or noninvasively, that are actually vulnerable and prone to subsequent rupture.[35–37] Where as FFR has been suggested as a method to improve patient selection, its use has not been shown to reduce mortality, as previously cited.[24,25]

PCI to Treat Angina

We also need to be realistic about how useful PCI is for treating angina.[18] If there is myocardium that is threatened by a flow-limiting stenosis or ruptured plaque that is amenable to PCI, then PCI may reduce or even eliminate angina. However, the inability to completely revascularize ischemic vascular territories owing to anatomic constraints may limit the utility of PCI for the treatment of angina. The correlation between symptoms and coronary artery– specific evidence of ischemia is low. In many patients, it is difficult to accurately discern which coronary stenosis is causing angina.

Furthermore, not all myocardial ischemia leading to angina is due to large-vessel (or epicardial) obstructive coronary disease.[38] There may be small-vessel or microvascular disease involving the coronary resistance vessels or arterioles that is difficult to recognize without careful testing.[39] Thus, some patients may not experience relief of their angina despite what appears to be excellent revascularization of 1 or more epicardial coronary arteries. Whereas dyspnea may be an anginal equivalent in some patients, it may not be easy to determine whether such symptoms are ischemic in origin, or a manifestation of physical deconditioning or chronic lung disease. In addition, not all chest pain is angina, and it is often difficult to distinguish angina due to myocardial ischemia from musculoskeletal or gastrointestinal pain. Finally, the psychological overlay to pain can make it difficult to assess and reliably treat angina with PCI.

The Way Forward

We need to avoid the “therapeutic illusion” that we are accomplishing more than is shown by the evidence.[40] Percutaneous coronary intervention for stable patients remains principally a treatment of limited benefit for angina, and probably no benefit for asymptomatic patients. Furthermore, the finite risk of complications (such as coronary dissection, stent thrombosis, MI, access site complications, and death) persists, such that the risk vs benefit analysis in the otherwise stable patient becomes tenuous.[8] Are we adequately counseling patients about the uncertain benefits but known risks prior to offering PCI?

In a provocative (if not prophetic) editorial by Braunwald[41] almost 40 years ago, physicians who readily adopted CABG to treat obstructive coronary artery disease were admonished not to perform revascularization in the absence of disabling angina or trial-based evidence that CABG could prevent cardiovascular events. The same can be said for PCI today.

Indeed, there is insufficient evidence to appropriately guide clinical decision making, even in selected, high-risk patients for whom one would expect an event rate reduction from PCI. The issue of whether PCI is more efficacious in patients with more severe ischemia is being studied prospectively in the National Heart, Lung, and Blood Institute–funded ISCHEMIA trial. However, ISCHEMIA will probably not be able to investigate the dynamic interplay between the extent and severity of ischemia and the presence of vulnerable plaques. In addition, ISCHEMIA will not be powered for the singular end point of mortality. With a primary composite outcome that includes nonfatal MI and cardiovascular mortality, ISCHEMIA may have similar limitations with the nonfatal MI component that has been a

source of criticism in COURAGE. Nonetheless, the ISCHEMIA trial is our best hope for obtaining additional, much-needed evidence to inform clinical practice.

A procedural therapy directed to just a few anatomic locations in the context of what is largely a diffuse and systemic atherosclerotic disease process involving the entire coronary vascular bed will likely be of inherently limited benefit. Medical therapy also contin-uestoevolve. It is largely life style and pharmacologic prevention that has resulted in the dramatic decreaseincardiovascularmortalityob-served over the past several decades.[42,43]

We need to come to terms with the realization that we do not have adequate scientific information for informed clinical decision making regarding PCI for stable ischemic heart disease. Even those who dismiss the findings from COURAGE and BARI-2D cannot cite data to support the widespread use of PCI as we have done for the past 20 years.[44]

Health Care Economics and Public Policy

Percutaneous coronary intervention is expensive. Mean Medicare hospital and physician payments are in excess of $15 000 per procedure.[45] For some 500 000 PCIs performed annually in the United States alone, the aggregate cost to payers computes to $7.5 billion dollars.[46] Payments from private insurance are higher and will result in a higher total. Note that the cost of PCI is in addition to the cost of medical therapy, which is needed in any case. With uncertain benefits and high costs, this can only be a low-value intervention at best, and a waste of money at worst. The cost-effectiveness analysis from COURAGE was not at all favorable for PCI as an initial management strategy.[47] Thus, the compelling question for professional societies and policy makers is whether there is sufficient evidence for the continued use of PCI as an initial management strategy, and based on the costs and resources used are we getting good value for the health care dollars we spend in treating patients with stable ischemic heart disease? The answer seems clear.

Until such definitive scientific evidence becomes widely available, patients, clinicians, payers, and health policy makers would be best served by adhering to the present body of evidence, namely, that for the majority of patients with stable ischemic heart disease, a “medical therapy first” approach to treatment, consistent with existing professional society guidelines, should be embraced.[48,49] Re-vascularization should be reserved for only those patients who ex-periencetreatmentfailureafteranadequatetrialofmedicaltherapy, whose anginal symptoms or quality of life deteriorate, or who have large areas of myocardium at risk demonstrated at low workload.

Clinicians often practice under conditions of considerable uncertainty, in which the results of clinical trials may not apply well to individual patients.[50] However, we must still strive to make the best decisions and therapeutic choices possible that are informed by, and conform to, existing clinical practice guidelines and appropriate use criteria.[26,49] As David Hume proffered almost 300 years ago, we should do well to ensure that we measure our beliefs and actions to the evidence that supports them.

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