Percutaneous Coronary Intervention Versus Medical Therapy in Stable Coronary Artery Disease

The Unresolved Conundrum

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One of the major dilemmas facing physicians is what diagnostic and therapeutic approaches should be recommended to those stable coronary artery disease patients whose symptoms are adequately controlled on medical therapy. This study sought to assess the evidence-based data relating to whether: 1) all patients with significant coronary lesions (i.e., ischemia-producing) should undergo percutaneous coronary intervention (PCI); 2) the best therapeutic approach is optimal medical therapy; or 3) PCI should be performed, but only in certain subsets of patients. We reviewed all recent meta-analyses of prospective randomized trials that compared the outcomes of medical therapy and PCI in stable, symptomatically controlled, coronary artery disease patients. To provide greater insights to the clinician, we then analyzed, in depth, 3 comprehensive and widely quoted randomized trials. Review of recently published (2012) meta-analyses, and the detailed analyses of 3 widely quoted individual studies, indicate no difference exists between PCI and medical therapy in nonfatal MI or in all-cause or cardiovascular mortality. Thus, clinical equipoise exists: in other words, there is no evidence-based justification for adopting 1 therapeutic strategy over the other. Therefore, it is not inappropriate, until additional evidence emerges, for the responsible, experienced physician to weigh several sources of information in formulating a recommendation to the patient, even though definitive evidence-based data are not as yet available. Such sources may include assessment of the individual patient’s clinical presentation, assessment of the severity of ischemia, and the patient’s precise coronary anatomy. Critical for more-reliable decision making will be future development of accurate measures of the individual patient’s risk of MI and/or death, whether by biomarker, imaging, or ischemia assessments. (J Am Coll Cardiol Intv 2013;6:993–8) © 2013 by the American College of Cardiology Foundation

Some major questions facing physicians responsible for the care of patients with stable coronary artery disease (CAD) whose symptoms are adequately controlled are: Should all patients with significant coronary lesions (i.e., those capable of producing ischemia) undergo percutaneous coronary intervention (PCI)? Or does evidence-based data indicate that the best therapeutic approach to such patients is ensuring they are on optimal medical therapy (OMT)? Or should PCI be performed, but only in certain subsets of patients? This paper discusses the complex issues involved in formulating a rational response to these questions given, as will become clear, that there are as yet no definitive answers.

Two fundamental pathophysiologic phenomena account for most clinical manifestations of CAD: 1) progressive plaque build-up in epicardial arteries, causing luminal narrowing—ultimately limiting the capacity to augment blood flow response to increases in myocardial demands, thereby causing
myocardial ischemia and thus angina; and 2) plaque rupture
causing intraluminal thrombus that occludes the vessel
lumen with consequent cessation of myocardial flow—
resulting in the most devastating consequences of CAD:
myocardial infarction (MI) and sudden death. Although
these 2 pathophysiologic processes are related, they also have
unique aspects, an understanding of which would help the
physician choose the most appropriate therapeutic strategy
for a given patient.

Although atherosclerosis is the background process neces-
sary for plaque rupture to occur, it is not a sufficient cause in
itself. Thus, many individuals with atherosclerosis, including
those experiencing myocardial ischemia, live into the late
decades of life without ever experiencing plaque rupture.
Others have MI early in their course, often without first
experiencing reversible ischemic symptoms, that is, angina. With the demonstration that distinct genetic differ-
ences mark patients with stable CAD versus those prone to
plaque rupture (1), it is likely that different pathways must be
activated for a stable plaque to become vulnerable to rupture.
Adding to the decision-making complexities is the critically
important observation that it is not necessary for an atheroscle-
rotic plaque to be significantly stenotic for rupture to occur (2–6).

Definitive evidenced-based data demonstrates that PCI per-
formed in the setting of acute MI reduces death and subsequent MI
(7). Our paper, however, focuses solely on the patient with symp-
tomatically controlled stable CAD and explores 2 major issues. First, does PCI reduce the incidence of MI and/or death, or is any derived benefit limited to relief of symptoms? This distinction in outcome definition is critical as if there is no penalty for delaying PCI until significantly limiting symptoms develop, then the case can be
made for delaying intervention, thereby avoiding the, albeit
small, risks posed by PCI. Second, if there is no clear benefit of
PCI on the incidence of MI and/or death, is it justifiable for the
responsible physician, when formulating a therapeutic
recommendation to the patient, to consider information for
which definitive evidence-based data are not as yet available?

Simple answers are not forthcoming. However, we believe
it is important to understand the unresolved issues and
appreciate how decisions will have to be made in the absence
of definitive evidence.

**Evidence From Recent Trials**

There have been, to the best of our knowledge, 4 recent (2012
to 2013) meta-analyses that reviewed all available trials of
patients with stable CAD in which patients were randomized
to medical therapy versus PCI, with the express intent of
determining whether PCI, when added to medical therapy,
 improves outcomes versus medical therapy alone (8–11).

Each meta-analysis reviewed 8 to 12 randomized trials,
and there was overlap in the trials analyzed. The uniform
conclusion of each of the meta-analyses was that there
was no difference in incident MI or death between the 2
therapeutic approaches (Table 1).

We decided that to further enhance the insights available
to the clinician, we would, in addition to presenting the
conclusions of these meta-analyses, critically review in
deepth 3 of the comprehensive and widely quoted ran-
domized trials: 1) the COURAGE (Clinical Outcomes
Utilizing Revascularization and Aggressive Drug Evalu-
ation) trial (12); 2) the FAME 2 (Fractional Flow Reserve
Versus Angiography for Multivessel Evaluation trial) (13);
and 3) the BARI 2D (Bypass Angioplasty Revascularization
Investigation 2 Diabetes) trial (14).

The COURAGE trial (12), published in 2007, showed that
symptoms improved more in patients with stable CAD
treated with PCI plus OMT versus OMT alone. However,
there was no difference between the 2 treatment groups in
the incidence of MI or death. The conclusions emerging
from these data were as follows: 1) PCI is justified if a patient
with stable CAD has symptoms sufficiently severe to com-
promise the quality of his/her life; and 2) it is not justified,
however, in such patients lacking limiting symptoms.

An important design component of the COURAGE trial
was that all candidates for recruitment had to undergo
coronary angiography, and it is likely that some patients were
excluded from the study because the responsible physician
decided that the patient’s anatomy posed an unacceptably
high risk without revascularization. Such decisions would have
excluded a subgroup of patients that might possibly have benefited from the revascularization procedure. As a corollary,
the COURAGE trial cannot be viewed as addressing the best
approach to diagnosis and treatment of stable CAD patients,
but rather as one testing relative treatment efficacy on a highly
selected group of patients—the group remaining once coronary
angiography is performed and patients were eliminated from
study entry consequent to those results.

Despite this, the question can still be raised: Was there
a subgroup of patients in the COURAGE trial at high risk
of acute MI or death that actually benefitted from revascular-
ization therapy—an effect masked by the total cohort
analysis? This issue is not unique to the COURAGE trial, as
virtually all large clinical trials have heterogeneous patient
populations such that certain subgroups might respond
differently from the majority of study patients. And, prac-
tically speaking, it is virtually impossible to prospectively
identify all possible subgroups.

The COURAGE investigators recognized this and
sought to determine whether the development of inducible

**Abbreviations and Acronyms**

- **CABG** = coronary artery bypass graft
- **CAD** = coronary artery disease
- **FFR** = fractional flow reserve
- **MI** = myocardial infarction
- **OMT** = optimal medical therapy
- **PCI** = percutaneous coronary intervention
- **VDUS** = virtual histology intravascular ultrasound
ischemia could identify such a subgroup. They reported, in a retrospective data analysis published in 2008 (15), that PCI more effectively reduced ischemia than OMT alone did and that ischemia improvement was associated with a trend to decreased events (death or nonfatal MI). Unfortunately, a more recent retrospective analysis of the COURAGE trial, examining the relationship between baseline stress-induced myocardial ischemia and clinical outcomes based on randomized treatment assignment (16), found that as a result of programming errors, the 2008 results “incorrectly reported a significant probability value with regard to worsening survival for OMT patients as compared with PCI + OMT for those with moderate to severe ischemia.”

In the updated analysis, patients were divided into those with no to mild (<3 ischemic segments) and moderate to severe ischemia (≥3 ischemic segments). The primary endpoint, death or MI, was similar in the OMT alone and the PCI + OMT treatment groups for all severities of ischemia. Thus, the COURAGE trial does not demonstrate that PCI performed in stable CAD patients with ischemia decreases death or nonfatal MI.

Nonetheless, retrospective reviews of registry data (17) support speculation that interventions improving ischemia should reduce cardiac events. Consequently, the COURAGE investigators have initiated such a trial—the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial (NCT01471522). This study randomizes stable CAD patients with moderate-to-severe left ventricular ischemia into 2 treatment subgroups: PCI + OMT versus OMT alone. The study may begin to resolve the conundrum of whether PCI should be performed in patients with inducible ischemia even if the severity of ischemic symptoms would not in itself warrant PCI. However, close to 90% of patients with stable CAD with no prior MI have ischemia involving <10% of the left ventricular myocardium, a value that would exclude them from entry into the ISCHEMIA trial (17). Thus, the results of the ISCHEMIA trial will not apply to the great majority of stable CAD patients who have lesser degrees of ischemia and who routinely form the basis for contemporary revascularization.

Although results from the ISCHEMIA trial are years away, another trial has just been published that also tested the concept that PCI performed in patients with ischemia will result in fewer cardiac events than will occur in patients treated with OMT alone. The FAME 2 trial (13) used fractional flow reserve (FFR), an index obtained by measuring pressures proximal and distal to the stenosis and then dividing the distal by the proximal pressure; the more severe the stenosis, the greater the pressure drop across it and hence the lower the FFR. FFR ≤0.80 is now commonly taken as functional evidence that lesions having such values are severe enough to produce ischemia and, therefore, are justified PCI targets.

The results of the FAME 2 trial validated the study hypothesis. The primary endpoint was a composite of death, MI, or urgent revascularization. Revascularization was defined as urgent when a patient was admitted to the hospital with persistent or increasing chest pain (with or without ST-segment or T-wave changes or elevated biomarker levels), and revascularization was performed during the same hospitalization.

Of 888 patients, 70 (8.4%) developed at least 1 primary endpoint event: 4.3% in the PCI group and 12.7% in the medical therapy group (p < 0.001). Most critically, however, the sole driving force responsible for the differences between the PCI + OMT alone groups was the rate of urgent revascularization (11% in the medical therapy group vs. 1.6% in the PCI group; p < 0.001). There were no differences between the 2 treatment groups in the incidence of MI and/or death. Although urgent revascularization is an important clinical endpoint, the fact remains that the increased need for urgent revascularization during follow-up

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<td>Pursnani, et al. (10)</td>
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CAD = coronary artery disease; CV = cardiovascular; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.
was not associated with a greater number of MI or deaths. It should be noted, however, that the incidence of MI and death was small (about 4% over the first year), suggesting that the trial probably did not have the statistical power to definitively test the effects of PCI on these endpoints.

Another issue arises because of study design. Patients and physicians were obviously not blinded as to whether a patient was randomized to PCI therapy. Therefore, it is likely that the responsible physician of a patient not assigned to the PCI group would more likely interpret any symptomatic change as needing urgent revascularization than if the patient had the prior “benefit” of PCI therapy.

Because the FAME 2 trial confirmed its primary composite endpoint, it could be concluded that PCI is indicated in all patients who have stenoses with FFR ≤0.80. However, an alternative therapeutic strategy can be considered: namely, deferring PCI for patients who have lesions with an FFR ≤0.80 until they need “urgent” revascularization. The rationale for this approach is that, first, in the FAME 2 trial, deferring PCI did not increase the rate of MI or death and, second, it spares from a seemingly unnecessary intervention the approximately 90% of patients who, despite having an FFR of ≤0.80, remain symptomatically stable and do not require urgent revascularization. Deferring PCI would also eliminate the small but definite risks incurred by PCI (18).

Such an approach is also supported by the fact that despite many trials, including the FAME 2 trial, PCI has not been shown to reduce the incidence of MI or death (14,19–21), a finding also reported in the meta-analyses noted earlier (8–11). One of the major trials testing this question prospectively was the BARI 2D trial (14). This was a complex randomized study in which diabetic patients with stable CAD were first separated, based on clinical considerations, into a CABG stratum and into a PCI stratum. Within each stratum, patients were randomized into a medical therapy group versus the particular revascularization strategy group. Primary endpoints were rate of death and a composite of death, MI, or stroke. Patients in the coronary artery bypass graft (CABG) stratum undergoing revascularization had significantly fewer major cardiovascular events over the 5-year follow-up than did patients in the CABG stratum assigned to medical therapy (p = 0.01). Although there was no difference in death rate, in the CABG stratum nonfatal MI occurred in 7.4% of patients undergoing CABG versus 14.6% in patients assigned to medical therapy. In contrast, the rates of cardiovascular events among patients in the PCI stratum assigned to revascularization versus medical therapy did not differ.

A possible explanation for why PCI does not appear to protect against future MI derives from studies in which coronary angiography was performed prior to a subsequent cardiovascular event—most prominently, the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial (6,22). Although the PROSPECT trial involved patients who presented with an acute coronary syndrome, we discuss it here because all patients underwent extensive 3-vessel coronary imaging studies after PCI of the culprit lesions (i.e., those lesions believed to have been responsible for the index event), and were then followed, thereby providing insight regarding the relation between specific lesion characteristics and subsequent events.

On follow-up, about one-half of the events that occurred were due to disease progression in a vessel judged at index catheterization not to be the culprit lesion; moreover, over one-half of these new culprit lesions had produced <70% obstruction at initial catheterization. Thus, many cardiovascular events occur consequent to progression or rupture of a plaque that at initial catheterization did not cause significant (>70%) obstruction. That angiographically nonsignificant stenoses could rupture and lead to MI was first reported in 1988 by Ambrose et al. (2) and by Little et al. (3) and subsequently reviewed and conceptualized (4,5). These investigators emphasized that plaques producing severe stenosis rupture more frequently than do plaques producing mild stenosis; however, because less obstructive plaques far outnumber severely obstructive ones, a high percentage of plaque rupture derives from plaques that produce mild obstruction.

Additionally, it is instructive to consider the predictive value of measures of the ischemia-inducing potential of a lesion, like FFR. That is, when the interventionist finds an artery with a lesion that has an FFR ≤0.80, how often will such a lesion lead to an event? In the FAME 2 trial (13), there were 625 lesions in the control group with an FFR ≤0.80; however, the total number of patients dying or experiencing an MI over 1 year was only 17 of 441. In other words, only 17 of 625 (3%) plaques that functionally were capable of producing ischemia actually went on to clinically evident rupture. Thus, the predictive accuracy of an FFR ≤0.80—that is, its ability to predict future plaque rupture—is extremely low.

These findings of the FAME 2 (13) and PROSPECT trials (6,22), as well as the studies demonstrating that plaque rupture commonly occurs in lesions producing mild obstruction (2–6,22), emphasize a critically important concept—that anatomic or functional severity of a stenosis, or lack of severity, is not a good way to predict risk of plaque rupture and, therefore, MI and death. They also emphasize, more generically, that the risk of future plaque rupture (as distinct from plaque progression leading not to MI but to progression of symptoms) is very low, even in patients presenting with acute coronary syndromes. Finally, the converse is also true: a subgroup of patients do not seem to experience angina even in the presence of severe stenosis or even MI (4,5). Thus, severity of symptoms cannot be used as a surrogate for risk of MI or death.
The Persisting Dilemma

If no more than 5% of patients studied in the catheterization laboratory for either acute coronary syndromes or stable CAD go on to develop over the next few years a life-threatening or myocardial infarction event, that is, plaque rupture, how can a therapeutic intervention, such as PCI, be justified as a wise therapeutic strategy if the large majority of patients in whom it will be performed do not develop the clinical syndrome for which the interventional procedure was intended? Especially if the intervention carries with it low, but nonetheless significant, risks? The dilemma becomes even greater when the fact that rupture frequently occurs from a plaque producing mild obstruction (and therefore would not have been the lesion targeted for PCI) is factored into the equation.

This formulation of the therapeutic dilemma indicates that there is a compelling need to shift primary focus from the anatomic or functional severity of a plaque to its vulnerability to rupture. Basically, the attempts to identify patients at high risk for developing plaque rupture involves 2 approaches.

The first involves invasive technologies to define the characteristics of plaques that are associated with a propensity to rupture. Initial excitement about the capacity of virtual histology intravascular ultrasound (VH-IVUS) to identify vulnerable plaques has moderated, given the results of the PROSPECT trial (16). In this study, 595 thin-cap fibroatheromas were identified by VH-IVUS; only 26 were sites of recurrent events at a median follow-up of 3.4 years (estimated cumulative event rate = 4.3%, or 1.3%/year). The trial also evaluated the predictive value of ultrasound-determined plaque burden of at least 70% (event rate 9.6%) and a minimal luminal area of 4.0 mm² or less (event rate 5.3%). When the data from all 3 modalities were present in a patient, the event rate rose to 18.2% over the 3.4 years; importantly, these events were mainly driven by rehospitalization due to unstable or progressive angina, as death from cardiac causes, cardiac arrest, or MI occurred with a cumulative 3-year rate of only 4.9%. Optical coherence tomography, with its high-resolution capacity, can identify thin-cap fibroatheromas, and the Infraredx catheter (Burlington, Massachusetts), with its capacity to identify lipid in plaques, are both promising modalities that might help identify plaques that are vulnerable to rupture. However, there are presently no natural history studies comparable to the data we have with VH-IVUS and FFR. Thus, none of the invasive imaging technologies currently available have as yet been shown to provide actionable clinical information about which plaques will rupture to guide therapeutic decisions.

The second approach to identify vulnerable plaque is the use of circulating biomarkers that can identify the “vulnerable patient.” Although many different biomarkers have been shown to identify stable CAD patients with increased risk, the absolute level of near-term risk is relatively low. However, a recent publication, analyzing for 3 biomarkers, each of which is involved in pathways associated with the development of vulnerable plaque, demonstrated that when 3 of the biomarkers are abnormal in patients with significant CAD, the risk of near-term MI or death is 18% (23). If these results are confirmed, such information could be used to define which patients with presumably stable CAD should be catheterized to determine whether high-grade proximal stenoses are present. As discussed previously, although such lesions by themselves do not provide sufficient reason for revascularization (with the exception of significant left main coronary stenosis or, perhaps, extensive 3-vessel disease [24]), the presence of a high-risk biomarker profile might well tilt the balance in favor of more aggressive therapeutic approaches.

Given that clinical equipoise exists (25)—that is, no definitive evidence exists proving the superiority of PCI versus OMT in reducing the risk of MI and/or death in patients with stable CAD—it is not unreasonable to incorporate into the decision-making process something commonly used in the daily practice of medicine—the judgment of the individual, experienced clinician. In this regard, 1 salient fact looms large when an individual patient is being studied in the catheterization laboratory—enormous anatomic and clinical variability exists from patient to patient: Does the lesion appear complex? Are there poor or excellent collaterals to the ischemic myocardium? Are there multiple coronary arteries significantly narrowed or only a single vessel? Although “stable,” have the patient’s symptoms actually been somewhat progressive? This variability of factors that may well influence outcome strongly suggests that a conclusion of clinical equipoise applicable to a total cohort may not apply to subgroups of patients or to individual patients.

The expert clinician, who frequently deals with this individual variability, gradually builds an experience leading to “clinical impressions”—these are not to be found in published databases and do not rise to the level of compelling evidence. And whereas any decisions made that are based on these impressions often prove to be wrong once the evidence of definitive randomized trials emerges, until such trials are completed, these judgments constitute an essential component of providing our patients with the best—albeit imperfect—available advice for therapeutic options.

Conclusions

It seems clear that in patients with a hemodynamically significant lesion and severe symptoms despite OMT, symptom control is a perfectly legitimate basis for recommending PCI (17). However, the conundrum arises in patients whose symptoms are adequately controlled but whose lesions are associated with ischemia (whether mild or severe). These patients have, at least anatomically, lesions that could be targeted by PCI. Rather than subjecting all such patients to PCI, with its attendant risks, it might be more reasonable to defer PCI until patients are in need of
revascularization based on their symptoms, because it does not appear that a penalty is paid if such a strategy is pursued. Thus, this “wait and see strategy,” as used for the medically treated patients of the FAME 2 trial: 1) did not result in a higher incidence of MI or death; 2) led to PCI being performed only in that small subgroup of patients who needed it during follow-up because of progression of symptoms; and, conversely, 3) led to withholding PCI from the large majority of patients who during follow-up remained clinically stable and did not develop any clinical indications warranting revascularization.

As discussed, however, the FAME 2 trial was prematurely terminated and not adequately powered to definitively determine that PCI does not reduce the incidence of MI or death. Thus, as is often the case in medicine, decisions have to be made in the absence of definitive data. Under these circumstances, the physician’s only recourse is to analyze the available information, come to what appear to be reasonable conclusions, discuss in depth the issues with the patient, and then, for physician and patient to make decisions that derive from the best, albeit limited, available data. The place of PCI in the management of many patients with stable CAD and without limiting symptoms falls into this category. Whether or not the specific decision made on the basis of careful weighing of incomplete data results in the right decision will be proven only by carrying out definitive studies.

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