The publication of the Clinical Outcomes Utilizing Percutaneous Coronary Revascularization and Aggressive Guideline-Driven Drug Evaluation (COURAGE) trial in March 2007 drew significant attention in the mainstream press and a flood of questions about the implications for how we treat heart disease. The COURAGE investigators concluded that patients with stable angina had the same likelihood of suffering myocardial infarction (MI) or dying regardless of whether they were treated with optimal medical therapy only or medications plus percutaneous coronary intervention (PCI).

Because interventionists have never claimed that patients who fit the COURAGE profile should undergo PCI in order to prevent death or MI, it was surprising to some that the study attracted attention. The media covered COURAGE for two key reasons: first, it was a large study presented at the American College of Cardiology (ACC) Annual Scientific Session and published simultaneously with its presentation in the *New England Journal of Medicine*; second, its main conclusion, that PCI “fails to reduce heart disease deaths,” although controversial, was stated prominently as the headline on the press release announcing the study’s findings (Figure 1).

More than most clinical trials, COURAGE demonstrates that intense media coverage can sometimes result in more confusion than illumination. Adding to the confusion were near-simultaneously reported studies indicating issues with late-stent thrombosis in some patients who had received drug-eluting stents (DES). These findings also received significant media attention before the scientific community had the opportunity to digest them and put them in perspective. As a result, interventional cardiologists report receiving numerous questions from both patients and noninterventional physicians about the implications of the COURAGE trial for the treatment of coronary artery disease. This article endeavors to look at how the COURAGE findings apply—or do not apply—to current healthcare for patients with chronic stable angina.

**DOES COURAGE MEAN THAT IT IS NOT NECESSARY TO CATHETERIZE PATIENTS?**

All of the patients in the COURAGE trial underwent diagnostic angiography before they were considered for enrollment in the trial. COURAGE researchers established very specific criteria in defining the “stable angina” patient they wanted to enroll in the trial. As part of the screening for enrollment in COURAGE, candidates had their coronary vascular anatomy delineated by coronary angiography.

Therefore, because all of the patients in the trial were catheterized, one cannot draw conclusions from the trial results about when to use diagnostic angiography. In fact, the majority of the patients subsequently excluded from COURAGE were excluded because of either clinical (had too much angina) or angiographic (high-risk anatomy) reasons.

**Figure 1.** An example of a title that sensationalized COURAGE and did not allow for more rational scientific discussion.
DID COURAGE FIND THAT PATIENTS WITH STABLE ANGINA DO NOT NEED PCI?

COURAGE showed that stable coronary patients already on an optimal drug program did not see a reduction in mortality or MI after they had received stents. The interventional community never expected in the present study this would be untrue. Additionally, with the natural history of coronary artery disease in this patient population, the study would be underpowered to show a benefit for PCI. Although it is undisputed that PCI saves the lives of patients who are experiencing MI and patients with high-risk “unstable angina,” PCI has never been promoted in any of the national treatment guidelines as saving lives or preventing heart attacks in patients with chronic stable angina.

Although drugs are the appropriate initial therapy for patients with stable coronary artery disease, there is a strong possibility that lifestyle limitation accompanying stable angina will prevent patients from achieving their recommended 30 minutes per day of exercise—a vital step in slowing down the progression of heart disease.

Compliance with the drug regimen required is also an issue. Studies have shown that compliance is inversely related to the number of medications prescribed. For example, it has been shown that when cardiac patients are expected to take three medications (aspirin, beta blockers, and lipid-lowering agents), compliance is as low as 21% (Figure 2). In COURAGE, patients were taking five medications but had dedicated nurses checking in on them every week or two, which certainly improved compliance. Although practitioners may desire to provide such support, such monitoring is unrealistic “in the real world.” It seems unlikely that patients could be so compliant with “optimal medical therapy” in clinical practice. Therefore, for many stable angina patients, especially those unable or unwilling to comply with a rigorous and costly drug regimen, PCI is the more effective long-term therapy. In fact, COURAGE showed that those patients who underwent PCI experienced less chest pain and took fewer medications specifically to treat stable angina symptoms than patients on medication alone.

To clarify: for many patients, PCI delivers relief from pain and discomfort and is the main reason that many patients, after discussion with their physicians, elect this option. This was clearly demonstrated in the findings of the COURAGE substudy examining quality-of-life after PCI versus optimal medical therapy. The substudy showed a marked benefit from PCI for stable angina patients for up to 2 years or more, especially for patients with the most frequent and severe chest pain. Patients who are relieved of such discomfort are much more likely to be able to resume normal lifestyle activities, including exercise, sooner and with far fewer symptoms than many patients who choose the medications-only route. It must also be noted that roughly one third of the patients in the optimal medical therapy group actually underwent PCI. In the sample size calculation for this study, it was estimated that 10% of the patients would cross over during this time interval. The subsequent improvement in angina in these patients actually confounds the comparison and suggests that the study may be underpowered to show a difference.

As with all treatment plans, determining the best therapy for an individual patient depends on knowing the patient’s condition and lifestyle goals. Although a drugs-only approach may be the right therapy for some patients (eg, a patient with a mostly sedentary lifestyle without significant ischemia on a stress test), it may not be appropriate for patients who desire an active lifestyle that includes activities such as playing golf, entertaining children or grandchildren, or participating in a symptom-free exercise regimen.

HOW SHOULD PHYSICIANS DECIDE IF OR WHEN ANGIOGRAPHY IS APPROPRIATE FOR A STABLE ANGINA PATIENT?

A key element in answering this question is to determine the significance of the patient’s ischemic burden. Although chest pain can result when there is not enough myocardial blood flow to meet the muscle’s needs, chest pain does not necessarily indicate ischemia. In fact, the mere use of nitroglycerin has been shown to increase the patient’s risk for subsequent events. The best way to measure the ischemic burden is through a stress test to determine how well the coronary arteries can deliver myocardial oxygen in the face of increasing demand to assess physiologic reasons for angina. The best imaging
stress test to be ordered should be determined by local expertise available for appropriate interpretation of results.

Patients with multiple risk factors, particularly if they are not optimally controlled, can benefit from diagnostic angiography as well because it will further risk-stratify and optimize their care. Determining if a patient has angina or ischemia can give clues as to what sort of symptoms they can expect in the future.

In addition to echocardiography and single photon emission computed tomography (SPECT) scanning, CT scans, positron emission tomography (PET) scans, and magnetic resonance angiogram (MRA) scans are being used at some centers for assessment of ischemic burden. They have not yet universally become first-line tools but are an important part of our armamentarium.

In summary, to decide whether angiography is appropriate, a combination of clinical evaluation of symptoms, functional testing, and imaging can help.

WHAT IS THE NEXT STEP FOR PATIENTS WITH STABLE ANGINA WHO PASS THEIR STRESS TESTS?

First, exercise stress tests are an important initial step in diagnosing the patient’s condition. It is important to remember that patients often tailor their lifestyles to their ability to handle exertion without pain, and they may do this without even realizing it. If a patient cannot walk for 6 minutes on the treadmill, then he or she probably becomes ischemic during normal activities of daily life. Patients may gradually cut back on activities if they feel uncomfortable doing them, and they may do this without consciously realizing that they are experiencing physical limitations. For example, they may avoid walking up stairs, circle the parking lot to find a space close to the store, have someone mow their lawn, or take a nitroglycerin tablet before walking up a hill. In other words, they accommodate the lack of blood flow. Many practitioners have observed a trend toward fewer exercise tests and more pharmacologic stress tests. Unfortunately, doing so limits the ability to consider the important physiologic changes that occur with exercise and stress testing, which provide additional prognostic data.

To simply ask the patient “How are you feeling?” or “Are you bothered by pain or shortness of breath?” may not reveal these lifestyle changes because the patient has already made the accommodations and, therefore, is feeling fine and is not bothered by pain or shortness of breath. This is why a 10-minute office visit may not be enough time to get adequate information about how the patient is doing and whether more testing or therapy is needed. Careful delineation of the patient’s functional capacity through objective questioning should be documented in the medical record. Significant decreases in function would increase the chance that angiography and potentially PCI would improve patients’ outcomes. Questions such as “How many blocks can you walk without pain?” “Are you still carrying your golf clubs, or are you using a cart now?” or “Are you doing less than you were 6 months ago?” assist practitioners in objectively determining worsening clinical symptoms.

WHAT ARE THE KEY TAKE-AWAYS FROM COURAGE?

First, let’s look at what are not the take-away points from COURAGE, an important task given that many in the media and medical community alike have unfortunately taken away the wrong messages.

It is important to understand that the main COURAGE trial looked at a very narrow group of patients, specifically those with stable coronary artery disease, who represent less than 30% of patients treated by interventional cardiologists. Of all patients who report they have coronary artery disease, only 7% actually undergo PCI.5,6 Clearly, PCI is not overutilized. Although COURAGE enrolled a large number of patients, those enrolled were a very homogeneous group. Most were men, and almost all had little ischemic burden and very manageable symptoms. They were at or near the target levels for the major risk factors when they were enrolled and, partly because of this, they were deemed capable of complying with an intensive drug regimen. Many received their medications at no cost to themselves and, as mentioned previously, had careful and frequent follow-up to ensure compliance and optimization of their risk factors. In addition, they had already undergone diagnostic catheterization that ruled out the urgent need for PCI.

Many of the patients like those seen in real-world normal daily practice were excluded from COURAGE. In
fact, the COURAGE population was relatively healthy and predominantly consisted of patients who were able to adhere to very strict medication and lifestyle-change requirements.

Next, COURAGE has been inappropriately distilled into sound-bite summaries proclaiming that PCI does not reduce death or MI. Many very important points, as well as findings from the trial, are lost in sweeping proclamations, including the fact that the ACC/American Heart Association/Society for Cardiovascular Angiography and Interventions practice guidelines have never suggested that PCI reduces the risk of death or MI in this population of stable patients. The headlines, therefore, ignore the reality that the main proposition tested by COURAGE was easy to knock down.

What’s more, to expect that PCI should reduce mortality or MI sets an unreasonably high goal because its enrollees—relatively healthy, stable patients—face a very small risk from either primary endpoint. To reduce that already very small risk would be especially difficult, and to truly demonstrate it would require a much larger study population.

In addition, the COURAGE trial did not consider that, given potential compliance issues related to the cost of medications or to the potential side effects of “optimal medical therapy,” many patients are not suitable for a medications-only approach. Because most patients in the US have to pay for part or all of their drug costs and do not receive the attention that the COURAGE patients did, compliance can be a significant issue in the real world. In contrast, of 2,287 patients enrolled in COURAGE, the vast majority came either from Canada or from a Veteran’s Administration hospital, and therefore did not have to pay for their medications; this likely improved their compliance.

Also, it must be noted that the vast majority of patients in the study—approximately 85%—were male, leaving open many questions about the extent to which the COURAGE trial is applicable to women given the significant differences in heart disease between the genders.

The COURAGE trial also did not address significant quality-of-life factors for the stable angina population. In consultation with their physicians, many patients choose PCI because it offers almost immediate relief from pain and discomfort, and they are much more likely to be able to resume normal lifestyle activities sooner with far fewer symptoms than many patients who choose the medications-only route.

Lastly, it is important to note that the nuclear substudy of COURAGE concluded that, even in these stable patients, PCI does save lives and prevent MI. This showed that patients with stable coronary artery disease, especially those with a moderate to severe case, gained significant long-term health benefits from PCI when compared with a drugs-only approach. The substudy showed that even a modest reduction in ischemic burden had a positive effect (Figure 3). The most appropriate goal for patients with stable angina is, of course, to enable them not just to live longer but to live better.

NOW THAT WE HAVE ADDRESSED WHAT NOT TO TAKE AWAY FROM COURAGE, WHAT SHOULD PHYSICIANS CONCLUDE FROM THIS STUDY?

First, PCI should be considered in symptomatic patients with significant ischemic burden. In stable angina patients who had moderate to large ischemic burden, mortality was decreased with PCI. This is a very important point, underscoring the importance of testing to reveal patients’ ischemic burden even if they are suffering relatively little angina.

Second, PCI improves quality of life, as demonstrated by the substudy of COURAGE. An improved quality of life allows patients to exercise more and practice healthy lifestyle modifications, thereby decreasing the incidence of further cardiovascular events.

HOW SIGNIFICANT IS IT THAT THE COURAGE TRIAL LOOKED AT AN OLDER STENT TECHNOLOGY NOW USED ONLY IN A MINORITY OF PCI PROCEDURES?

It is true that most of the stents used in COURAGE were bare-metal stents (BMS). Only a very small minority of the patients in COURAGE was treated with DES, and even that was during our early experience with these devices.

The COURAGE trial was presented in early 2007, during a time when some studies raised the issue that in a small fraction of patients (0.5% of the total), DES were associated with late-stent thrombosis. Since that time, it has been shown definitively that this risk is greatly reduced if the patient complies with a regimen of dual-antiplatelet therapy for at least 1 year and that the incidence overall is no different than that seen with BMS; only the timing and mechanism are different.

Recent studies have shown that DES therapy is unquestionably a superior therapy to BMS for most patients. There is, in general, a 50% reduction in restenosis in DES patients and, consequently, a 50% reduction in the number of repeat PCI procedures. In the June 25 issue of the Journal of the American Medical Association, Malenka et al showed that the widespread use of DES over BMS in recent years has led to a significant decline in...
the need for repeat procedures to unblock coronary arteries and that DES do not increase the risk of death compared with BMS.9

By implication, it is then reasonable to suggest that, if DES had been used in COURAGE, the outcomes of the study and its substudies might look quite different. New data even suggest mortality may be improved with DES, even in stable patients.10 By reducing restenosis, subsequent angina would also be reduced, and the benefit of PCI would likely be prolonged. In a recent cost-analysis substudy of COURAGE, it was found that PCI was more expensive than optimal medical therapy; however, this substudy also fails to acknowledge the potential impact of new DES technology.11 Consider the possibility of 50% fewer repeat procedures, and the effect of the 30% of patients in the medicines-only treated group who underwent PCI (again with BMS); is it not likely that the calculations would look quite different? Furthermore, because there was no difference in mortality (as anyone would expect), there is no possible way for the COURAGE strategy to demonstrate potential cost effectiveness for PCI.

When Should a Patient With Stable Angina Be Referred to an Interventional Cardiologist?

Upon diagnosing a new coronary artery disease patient, the general cardiologist or primary care physician typically urges risk factor modification and prescribes medical therapies, such as low-dose aspirin, clopidogrel, beta blockers, and/or statins. This strategy complies with the ACC/American Heart Association guidelines for maximizing therapy.12 If it appears that the conservative medical approach is not working, that target levels of all the modifiable risk factors are not achieved (the premise of COURAGE), or that the patient is unable to comply with that approach, the primary healthcare provider should consider referring the patient to an interventional cardiologist.

Importantly, referral to an interventional cardiologist does not mean the primary care physician or general cardiologist is “losing” the patient. The role of the interventional cardiologist is to help determine the best treatment, depending on the patient’s condition, health, and lifestyle goals and to help weigh the risks and benefits of potential treatment options, whether it be medications only, PCI, or coronary artery bypass graft.

For the patient with stable angina, the choice may depend on lifestyle goals. Many patients only on medication may be dissatisfied or concerned by the debilitating pain and limitations associated with their disease and want to resume an active lifestyle. Because PCI often immediately relieves these symptoms, this approach may be a good option.

It is particularly important that, for these patients, the primary care providers, general cardiologists, and interventional cardiologist work together to monitor for symptoms of subsequent lesions, to help encourage patient drug compliance, or to determine if further procedures are necessary.

Comprehensive, long-term care for the coronary artery disease patient depends on a strong collaboration between the primary care physician, general cardiologist, and interventional cardiologist. Together, they can determine how to most effectively manage the disease through appropriate best-practices methods.

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