Percutaneous Coronary Intervention for Chronic Stable Angina

A Reassessment

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As it approaches its fourth decade, percutaneous coronary intervention (PCI) is now the most widely used revascularization strategy around the world and has been tested in multiple clinical scenarios against both medical and surgical therapies. For each patient group and clinical scenario setting, the goals of therapy must be specifically defined and clearly understood as an integral component of the process of selecting the optimal strategy for the individual patient. In patients with chronic stable, often mild angina, the major achievable goals of PCI are to affect symptoms, either by decreasing them or preventing them, reduce the need for subsequent procedures, and relieve ischemia. Achievement of these goals has been documented in multiple randomized trials of PCI versus medical therapy. In these trials of patients with stable coronary artery disease (CAD), however, no reduction in death and myocardial infarction has been observed, and these limitations of PCI in this clinical setting need to be emphasized. Given the typically diffuse nature of CAD and the fact that PCI only treats a segment within a coronary artery, this is not surprising. Although optimal medical therapy forms the cornerstone of management for any patient with CAD, among stable patients who do fail medical therapy, percutaneous coronary revascularization plays a well-documented significant role in improving symptoms and preventing the subsequent need for revascularization. The appropriate utilization rates of PCI in patients with chronic stable angina and preserved left ventricular function should lead to more cost-effective care of patients with stable CAD. (J Am Coll Cardiol Intv 2008;1:34–43) © 2008 by the American College of Cardiology Foundation

It has been 30 years since Gruentzig first used a percutaneous procedure to treat a patient with coronary artery disease (CAD) (1,2). In that initial application, a 37-year-old male with unstable angina pectoris of recent onset underwent successful balloon dilatation of a proximal left anterior descending lesion. In 2000, at the age of 61 years, that patient had recurrent chest pain for the first time since the initial procedure. Angiography documented no significant stenosis at the site treated in 1977.

Over the course of the past 3 decades, there have been major advances in nonsurgical coronary revascularization, and percutaneous coronary intervention (PCI) has now become the most widely used revascularization procedure around the world. Although a substantial part of this growth has been the consequence of the well-documented improvement in outcomes of patients with the broad spectrum of acute ischemic syndromes who undergo PCI versus medical therapy (3–7), it is primarily the result of the application of PCI in patients with chronic coronary disease who have either stable angina or a positive functional test.
with ischemia. On one hand, the burgeoning use of PCI is understandable because of major technological advances in the field, but it should be appreciated that, although PCI has taken the place of coronary artery bypass grafting (CABG) as the most widely used mode of revascularization, the major increase in the utilization of PCI has been because of its use in patients formerly treated with medical therapy only. Patients and physicians frequently view coronary artery stenosis as a mechanical problem to be “fixed” by mechanical means. Nonetheless, during the last few decades, there have also been profound improvements in approaches to primary and secondary prevention, and these sentinel advances in medical therapy have generated new questions about whether PCI may be overused as the initial therapeutic approach to patients with stable CAD and relatively mild symptoms. The consistent findings in generations of trials comparing PCI and surgical revascularization with medical therapy, together with recent advances in secondary prevention, set the stage for a reappraisal of the critically important issue of optimal management of patients with chronic stable angina.

This discussion of therapeutic modalities needs to be considered in relation to the overall goals of therapy in chronic CAD. In this respect, the chronicity and progressive nature of the disease processes are of paramount importance. Coronary disease is not cured by any currently available therapies, but the natural history and prognosis may be modified. This is germane to all therapeutic strategies, namely medical therapy, PCI, and surgical revascularization. Potential targets of therapy include short- and long-term goals that vary from prevention of clinical events to the treatment of symptoms (Table 1).

The application of PCI in an attempt to achieve these goals depends upon many factors, including the extent and severity of the CAD, the baseline demographics of the patient (including comorbidities), and the patient’s presentation (e.g., an acute ischemic syndrome versus stable angina versus asymptomatic ischemia). The benefits of coronary revascularization in patients with ST-segment elevation myocardial infarction (STEMI) and non–STEMI acute coronary syndromes (ACS) have been the subject of multiple trials, with the general consensus favoring an aggressive mechanical approach in patients with these syndromes and, in particular, among those at higher risk (3–7). The present discussion will focus on patients with chronic stable angina, not on patients with ACS.

Irrespective of whether revascularization is performed surgically or percutaneously, the landscape has changed irrevocably in that aggressive secondary prevention is an integral aspect of management. This has been an area of intense investigation, and there are robust evidence-based sets of data that have been used to formulate guidelines for optimal care, which emphasize the benefits of aggressive risk factor modification with diet, exercise, and treatment of obesity, diabetes, hypertension, and hyperlipidemia, as well as tobacco cessation. Specific adjunctive medical therapies should include administration of statins, aspirin, an angiotensin-converting enzyme (ACE) inhibitor in many but not all patients, and the judicious use of nitrates and beta-blockers and calcium channel blockers in symptomatic patients. Blood pressure control may require multiple drugs, and some lipid abnormalities require interventions beyond statins. Control of hyperglycemia has been proved critical in managing diabetes. New antianginal agents are under development, and one such drug, ranolazine, has been approved recently by the Food and Drug Administration (FDA) (8–10).

Consideration of the goals of PCI must take into account the description of what would be considered to be “optimal PCI.” The technological revolution, dominated by stent implantation and advances in antithrombotic and antiplatelet therapies, is continuously evolving. As a direct consequence, there has been a dramatic decrease in the need for urgent CABG surgery following PCI because the problem of acute or threatened closure has been almost eliminated. In addition, bare-metal stents (BMS) have reduced, although not eliminated, clinical or angiographic restenosis and the need for repeat revascularization procedures (11–14). Nonetheless, it should be emphasized that two decades of studies have not shown that conventional percutaneous transluminal coronary angioplasty (PTCA) improves survival in comparison with medical therapy (15–20) (Fig. 1). Given the change from balloon dilatation to stent implantation, it is important to evaluate the effect of stenting on the hard end points of death and myocardial infarction (MI). Two separate meta-analyses have been

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<th>Table 1. Goals of Treatment</th>
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<tr>
<td>Relief or decrease of angina and ischemia</td>
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<td>Prevention of progression of disease</td>
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<td>Prevention of complications of disease including myocardial infarction</td>
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<td>Worsening left ventricular function or development of congestive heart failure</td>
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<td>Cardiovascular death</td>
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<td>Sudden cardiac death or arrhythmias</td>
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**Abbreviations and Acronyms**

- **ACE** = angiotensin-converting enzyme
- **ACS** = acute coronary syndromes
- **BMS** = bare-metal stent(s)
- **CABG** = coronary artery bypass grafting
- **CAD** = coronary artery disease
- **DES** = drug-eluting stent(s)
- **FDA** = Food and Drug Administration
- **LV** = left ventricular
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **PTCA** = percutaneous transluminal coronary angioplasty
- **STEMI** = ST-segment elevation myocardial infarction

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published (Figs. 2 and 3). Brophy et al. (21) found no difference in death or MI between balloon angioplasty and stenting in 29 trials involving 9,918 patients. Al Suwaidi et al. (22) performed another meta-analysis of 23 trials that included 10,347 patients. This meta-analysis demonstrated no significant difference between the techniques in the frequency of death or MI. There was, however, a significant reduction in major adverse cardiac events. This was solely the result of a reduction in target vessel revascularization.

The subsequent development and widespread adoption of drug-eluting stents (DES) further improved the outcome of percutaneous procedures by significantly reducing restenosis compared with BMS. In multiple series, the need for subsequent procedures with DES has been reduced to single-digit frequency. Recently, the issues of stent thrombosis have attracted considerable attention and generated controversy (23–28). However, the data as a whole still support the following conclusions (Figs. 4 and 5):

1. Drug-eluting stents significantly reduce restenosis compared with BMS.
2. Overall stent thrombosis rates are low and occur with both BMS and DES.
3. The timing of stent thrombosis appears to vary; stent thrombosis with DES appears to occur somewhat later than with BMS and may continue for a longer period of time. Moreover, stent thrombosis is an unpredictable event and is associated with severe consequences. Cessation of clopidogrel is an important precipitating factor, but other mechanisms must be operative in many patients.
4. In carefully selected patient populations in the randomized trials leading to FDA approval, there was no difference in death or MI during follow-up, irrespective of whether BMS or DES were placed. This, however, is not a universal finding, and there appear to be differences between trial and registry populations, particularly those including patients with non-FDA-approved indications for DES. For example, the DEScover registry enrolled 6,906 patients undergoing PCI at 140 medical centers from January 2005 to June 2005. At 1 year, there was no difference in the adjusted risk of death or MI between DES and BMS. There were, however, no differences in the rate of stent thrombosis. This is in contrast to the Swedish Registry, which did not find a difference in death and MI during 3 years of follow-up. However, there was a difference in the temporal profile, with more adverse events in the first 6 months with BMS and more events after 6 months with DES. More data are needed particularly among higher-risk patients who were excluded from the initial randomized trials.

5. The optimal duration of dual antiplatelet therapy with clopidogrel needs to be determined.

Optimal percutaneous approaches demand attention to antithrombotic and antiplatelet therapies (both periprocedural and after discharge) and multiple technical issues related to the placement of the stent; these include the appropriate size and length, selection of equipment, implantation techniques, and an awareness of comorbidities and their potential interactions with the procedure (e.g., renal failure, diabetes, and severe left ventricular [LV] dysfunction).

Recent trials of PCI versus medical therapy (COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation]) and the MASS (Medicine, Angioplasty, or Surgery Study)-2 trial of PCI, CAGB, and medical therapy have generated considerable interest and again draw attention to the issue of the appropriate indications for coronary revascularization and particularly PCI in patients with chronic stable angina. In many respects, the findings of these contemporary trials should not come as a
surprise because these are entirely consistent with the majority of prior trials over a 20- to 30-year period. In this respect, a review of the results of previous randomized trials in patients with chronic stable angina may help in placing the recent trials into perspective.

Early trials in the 1970s and 1980s of CABG versus medical therapy compared CABG during the learning curve of this procedure with medical therapy that would be considered entirely inadequate by today’s standards. Nonetheless, the evidence-based data from these trials suggested a survival benefit only for surgery patients at medium or higher risk, including those with LV dysfunction and multivessel disease. In patients with preserved LV function and stable angina Canadian Cardiovascular Society Class 1 to 2, there was no mortality benefit with surgery over medical therapy. Subsequent registry studies demonstrated quite clearly the survival benefits of revascularization only among patients with severe symptoms and multivessel disease irrespective of LV function (29).

The next series of trials compared PTCA with medical therapy in patients with stable angina. A recent meta-analysis demonstrated a lack of benefit in death and MI from PCI (15,18,19,30) (Fig. 1). Nonetheless, these studies did convincingly identify greater relief of symptoms with revascularization. More recent studies that included patients with stents were TIME (Trial of Invasive versus Medical therapy in Elderly patients) in elderly patients with severe angina randomized to revascularization with either PCI or CABG versus intensive medical therapy (31); the MASS-2 trial, which had three arms (CABG, PCI, or medical therapy) (32); and the AVERT (Atorvastatin VERSus Revascularization Treatments) trial of medical therapy versus PCI (19). In the AVERT trial, lipid lowering was less aggressively performed in the interventional arm. None of the trials demonstrated an advantage of revascularization over medical therapy in regard to death and MI. However, in many trials, up to 50% of patients “crossed over” to revascularization with PCI or CABG due to persistent symptoms that were refractory to antianginal drug therapy.

An important early trial was the ACIP (Asymptomatic Cardiac Ischemia Pilot) study of 558 patients with clinically stable, angiographically documented CAD who were judged suitable for revascularization after being diagnosed with silent ischemia on 48-h Holter monitoring (33). Three strategies were tested: 1) angina-guided medical therapy; 2) angina plus ischemia-guided therapy; and 3) revascularization using either surgery or PTCA. In contrast to the studies above, total mortality, the combined end point of death or MI, and the end point of death, MI, or recurrent cardiac hospitalization were significantly decreased in patients undergoing revascularization. This was a pilot study and emphasizes the importance of designing and implementing larger adequately powered trials. Similar results were found in the SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) trial, a small trial of 201 patients with a prior MI and silent ischemia, which found a benefit for PCI in regard to recurrent events over a 10-year follow-up period (34). Thus, it may be that, among the large number of patients with stable CAD, those with silent ischemia may be a high-risk group that can benefit from PCI.

In summary, 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 in the “hard” end points of death and MI; and 2) in patients on medical therapy, crossover to revascularization is frequent. Therefore, in many patients, a trial of medical therapy is very appropriate, with the understanding that if symptoms and quality of life are not improved, the option of revascularization may be chosen, and the price to be paid is not that of an increased rate of death or MI. These data set the stage for a critical discussion of the most recent trial (COURAGE) (35), which has generated considerable emotion and some controversy. The question to be addressed is whether the results should have come as a surprise.

The COURAGE Trial

As has been true with almost all randomized trials of medical therapy versus a revascularization strategy, many more patients were screened than randomized. In the COURAGE trial, 35,539 patients were initially screened, and 3,071 met eligibility criteria; of these 3,071 patients meeting eligibility criteria, 2,287 were enrolled. It must be remembered that all randomized trials are subject to “entry bias.” This precept stands in contrast to registries, which are characterized by “selection bias.” The underlying hypothesis in the COURAGE trial was that a strategy of PCI with optimal medical therapy would reduce the risk of death and nonfatal reinfarction compared with optimal medical therapy alone. The 3-year event rates were projected to occur in 16.4% of the PCI plus medical therapy group versus 21.0% of the medical therapy group. The actual event rates were 19% in the PCI group and 18.5% in the medical therapy group.

Crucial to the understanding of this trial is an appreciation of the baseline characteristics of the patients enrolled. Even though not all patients enrolled were at very low risk, the trial was aimed at patients with stable disease and not acute ischemic syndromes. Baseline characteristics of the enrolled patients included: 1) 42% to 43% of patients had either no angina or only class 1 angina; 2) 30% of patients had single-vessel disease, and approximately 35% had disease involving the left anterior descending; 3) the ejection fraction was approximately 61% in both groups; and 4) DES were not routinely available.
In a patient such as was recruited for this trial, it is unlikely that any revascularization strategy would improve the rate of death and MI. With an 8% mortality rate at 5 years and only 27% of those deaths being due to cardiac causes, it would also be unlikely to show or expect a mortality difference. Moreover, the rate of death, MI, and stroke is approximately 20% and very unlikely to demonstrate a difference because neither noncardiac mortality nor rates of stroke would be expected to be reduced by PCI. Consequently, the only modifiable hard end point would likely be MI and probably Q-wave MI because biomarker elevation occurs frequently after stenting. As previously discussed, only in patients at higher risk does revascularization with PCI or CABG result in a reduction in death and MI. Even with the advent of DES, multiple randomized trials and registry studies have not documented a reduction
in the hard end points of death or infarction compared with BMS (23–25).

Given the inability of PCI to dramatically decrease death and MI in this patient population with stable symptoms, relief of symptoms and prevention of the need for clinically driven subsequent procedures remain more important from a patient standpoint. In the COURAGE trial, angina relief was better and quicker in the PCI group. Subsequent revascularization in the medical group was performed for “angina that was unresponsive to maximal medical therapy or when there was objective evidence of worsening ischemia on non-invasive testing.” Any subsequent revascularization in this trial was therefore clinically driven and not related to a protocol requirement. PCI showed a significant advantage over medical therapy, with a subsequent revascularization rate of 21.1% versus 32.6% in the optimal medical therapy group (hazard ratio 0.60, 95% CI 0.51 to 0.71, p < 0.001). Based on the documented reduction of restenosis with DES compared with BMS, it is reasonable to speculate that the revascularization rates in the PCI group of the COURAGE trial would have been likely significantly less had DES been used. What was surprising and gratifying in the COURAGE trial, however, was the high rate of angina relief among medically treated patients. This may be the result of superb adherence to protocol-driven medical therapy. In the optimal medical therapy group, at 3 years, 75% of patients were on an ACE inhibitor or angiotensin receptor blocker, 92% were on a statin, 86% were on a beta-blocker, and 50% were on a calcium channel blocker. Similar adherence to medical therapy was also present in the PCI group. This degree of adherence to evidence-based therapy is infrequent in registry series (36).

Accordingly, we could conclude that in the group of patients with stable angina and generally well-preserved ventricular function (ejection fraction approximately 61%), the application of PCI in addition to optimal medical therapy results in improvement of symptoms and a significant decrease in the need for subsequent revascularization in
many patients. There are several explanations for the lack of benefit 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 of 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 treated medically, collateralization may play a role in alleviating symptoms, although collaterals are generally an indication of severe ischemia.
5. Acute coronary syndromes secondary to ruptured plaques occurs frequently at sites separate from areas of severe stenosis, regardless of initial PCI. This observation is also true for patients receiving optimal medical therapy alone.

Potential for overuse of PCI. Given that PCI in patients with chronic stable angina is very effective in improving symptoms but has not been shown to decrease death or MI, why
has there been such controversy about the potential for overuse? Data from both Europe and the U.S. demonstrate marked regional variations in the rates of PCI use, suggesting that factors other than “evidence-based” medicine are playing a role. For example, in a recent study of 11 states in the U.S., variations in procedures performed per capita were 1.83-fold for PCI and 1.54-fold for CABG. Variations in the rate of cardiac catheterization accounted for 68% of the variability in rates of revascularization, and major independent determinants of catheterization rates were the number of cardiac surgeons and interventional cardiologists in a particular state (37). Thus, it seems that this complex issue of potential overuse of PCI has multiple components, including overuse of angiography, noninvasive coronary angiography, fear of litigation, financial incentives for providers, and self-referrals.

The variability in the rates of coronary angiography in North America and Europe is also quite striking. A single unified explanation to account for this is not readily available (38–40). Reasons may include access to catheterization laboratories and availability of cardiologists, patient expectations, the preference of the primary caregiver, the extent and application of specific screening approaches, and implementation of evidence-based guidelines.

Patient desire for a “quick fix,” defensive medicine, and a lack of understanding of therapeutic choices are additional confounders. This issue may become more problematic with the increased application of noninvasive computed tomography-based coronary angiography that may identify lesions in patients who are asymptomatic. When lesions have been identified with noninvasive coronary angiography and patient reassurance becomes more difficult, this can be the catalyst for a cascade of events including coronary angiography and intervention.

Prior to invasive coronary angiography, there is often a discussion with the patient regarding the course of therapy in the event that a significant lesion or lesions are found. The scene is often set for percutaneous treatment if the lesion is deemed suitable. From the patient’s standpoint, this makes intuitive sense to combine the diagnostic angiogram and the intervention in a single setting. This “convenient” approach to treat what is there has become ingrained and is part of both patients’ and physicians’ expectations. Nonetheless, the consequence may be the lost opportunity to discuss all the therapeutic options in a less urgent setting and with all the information at hand.

To further complicate matters, payers in some regions have insisted that only interventionalists perform diagnostic catheterizations so that any lesion found may be stented at the time of the diagnostic procedure. The complex but real issues of financial incentives and self-referral cannot be ignored and are an integral part of this discussion. Self-referral eliminates some of the checks and balances that are a healthy aspect of the decision to choose among many effective options. Likewise, cost-effectiveness is an important component. Claude et al. (41) analyzed this in elderly patients with chronic angina. Patients undergoing an invasive approach had higher 30-day costs but lower 2- to 12-month hospital and interventional costs than medically treated patients. Medical patients had higher practitioner charges.

**Conclusions**

What then can be said about the role of PCI in the current era? First and foremost, in patients with stable angina and in general well-preserved LV function who are beginning or are already on optimal medical therapy, application of PCI does not reduce the frequency of subsequent MI or cardiac death; it does, however, significantly reduce angina. PCI also reduces the need for subsequent additional procedures. An appropriate approach is to initiate a trial of medical therapy and aggressive risk factor reduction in patients with mild stable angina who are amenable to this strategy, cushioned by the security of knowing that a subsequent crossover to PCI does not come at the price of increased death or MI. A crucial aspect of this discussion is a thorough understanding of the patient’s realistic expectations: the impact of angina upon lifestyle and the ability to tolerate medical therapy. Moreover, comprehensive secondary prevention remains the bedrock of both strategies.

Second, DES have been found to be associated with significant reduction in restenosis and thereby may further improve anginal relief in both stable and unstable patients. The issue of stent thrombosis continues to require further study, as does the most appropriate duration of dual antiplatelet therapy.

Finally, the appropriate rates of use are a major concern with important socioeconomic implications. What is needed is to establish whether use is appropriate, and, if not, why not? It is up to the cardiovascular community to ensure that evidence-based medicine dominates clinical practice. The Clinical Competence Statement on Interventional Cardiology of the American College of Cardiology, American Heart Association, and Society for Cardiac Angiography and Interventions advances suggestions for maintaining quality and ensuring appropriate selection of these procedures (42). The credibility of what we as cardiologists do and how we implement coronary revascularization places the onus of responsibility on us.

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